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BULLETIN

OF THE NEW YORK ACADEMY OF MEDICINE

Original Articles by

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ALVAN L. BARACH

JOHN J. TOOHY

THE USE AND ABUSE OF IRON THERAPY AND TRANSFUSION

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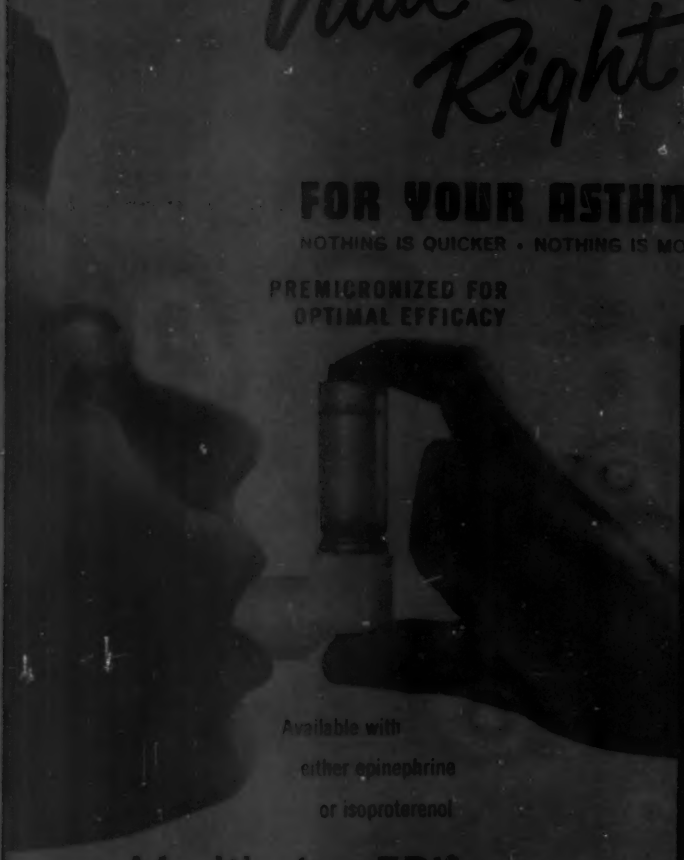

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References: 1. Graham, W.: Canad. M. A. J. 79:634 (Oct. 15) 1958. 2. Robins, H. M.; Lockie, L. M.; Norcross, B.; Latona, S., and Riordan, D. J.: Am. Pract. Digest Treat. 8:1758, 1957. 3. Kuzell, W. C.; Schaffarzick, R. W.; Naugler, W. E., and Champlin, B. M.: New England J. Med. 256:388, 1957.

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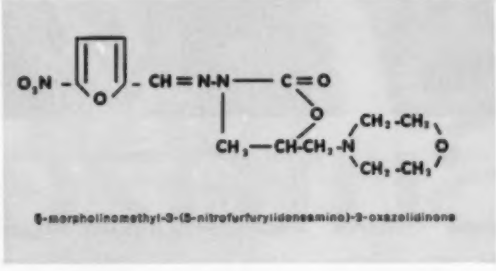

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*Carter, S.: M. Clin. North America 31:1 (March) 1953.

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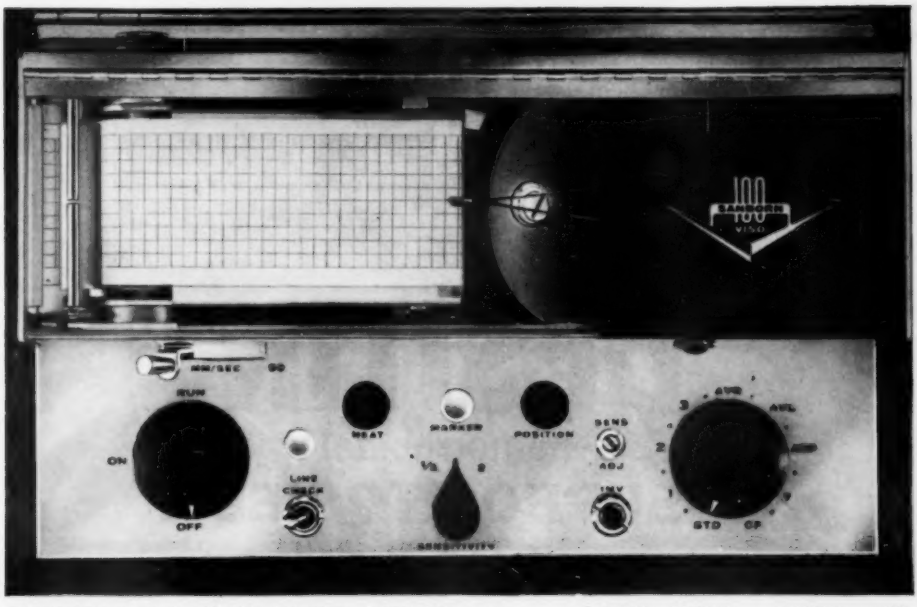

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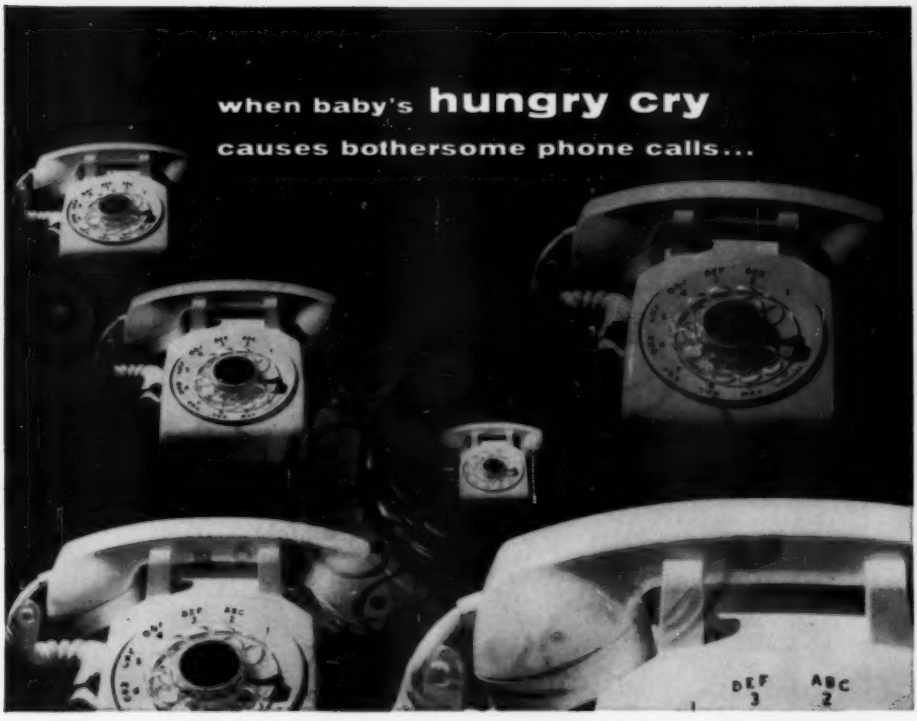

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1. Hatfield, H. A.; Simpson, R. A., and Jackson, R. L.: J. Pediat. 44: 32-45 (Jan.) 1954. 2. Frost, L. H., and Jackson, R. L.: J. Pediat. 39: 580-582 (Nov.) 1951. 3. Haeryksson, W. E.: GP 8: 51-56 (Oct.) 1953. 4. Lichtheim, H. R.: Arch. Pediat. 61: 617 (Dec.) 1944.

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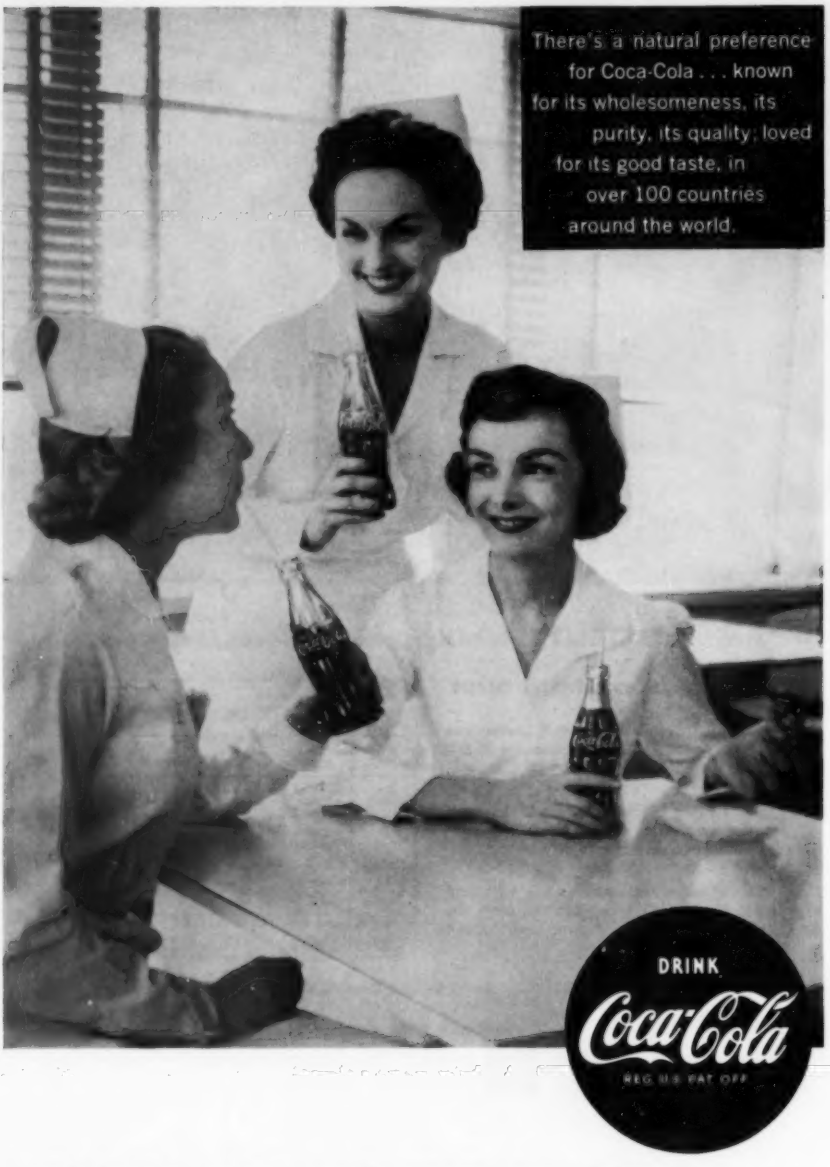

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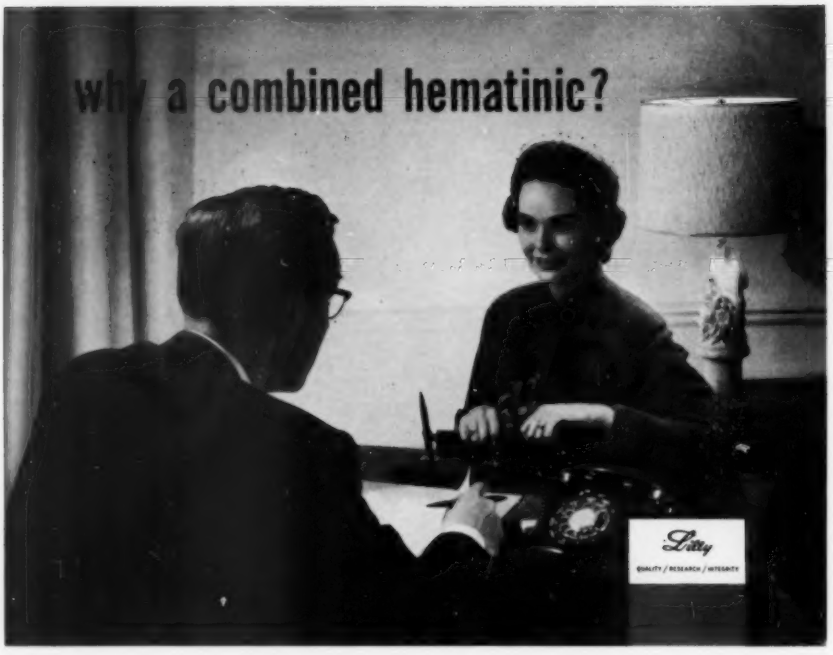

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1. A. M. A. Arch. Int. Med., *99*:346, 1957.
2. Am. J. Obst. & Gynec., *70*:1309, 1955.
3. Lancet, *1*:448, 1957.

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ROBERT L. CRAIG, *Editor*

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BULLETIN OF
THE NEW YORK ACADEMY
OF MEDICINE

VOL. 35, NO. 8 AUGUST 1959

OCCLUSION OF THE ABDOMINAL AORTA AND DYSFUNCTION OF THE SPINAL CORD*

A CLINICAL SYNDROME

ALBERT W. COOK

SPONTANEOUS occlusion of the abdominal aorta as a clinical entity is usually accompanied by varying degrees of impaired blood supply to the lower extremities. The abnormal clinical features under these circumstances may be predominantly those of intermittent claudication, manifestations of peripheral neuropathy or ischemic necrosis of regional tissue. These syndromes may appear rather acutely or have a more prolonged progressive onset depending upon the nature of the occluding agent, whether embolus, thrombus or simply atheroma. Since the more obvious features are related to vascular embarrassment in the lower limbs, except in spontaneous dissection of the aorta, rarely has attention been directed to dysfunction of the spinal cord. It is our purpose to present another clinical syndrome, that of dysfunction of the lower spinal cord associated with occlusion of the distal aorta but without

* Presented, in part, at the Combined Meeting of the Section on Neurology and Psychiatry with the New York Neurological Society, at The New York Academy of Medicine, October 9, 1958.

From the Division of Neurosurgery, State University of New York Downstate Medical Center at Brooklyn, and the Neurosurgical Service of the Kings County Hospital in Brooklyn, New York.

marked clinical impairment of circulation in the lower limbs. The essential features of the syndrome are as follows: There is rather rapid onset of varying degrees of paraparesis, the most cephalad part of the spinal cord implicated being from the seventh to the ninth thoracic segment. Significant alteration in appreciation of pin prick is present below this level and may be more evident on one side. Proprioceptive sensibility may or may not be disturbed. Areflexia or hyporeflexia is often present in the lower extremities and may persist. Bilateral Babinski signs are present in addition to incompetent vesicle and anal sphincters. Considerable pain of a radicular nature is most often present in the lower extremities. Plane roentgenograms of the spine do not disclose any abnormality, and the spinal subarachnoid space is found to be patent after a Queckenstedt test and myelography. Chemical and cellular examinations of the spinal fluid usually show normal results. After some time in the course of the illness, exploratory laminectomy has been done without disclosing the nature of the spinal cord lesion. Gradually, over a period of time, the level of altered sensibility regresses and may disappear. Muscle reflexes in the lower extremities may return to normal, yet areflexia may persist. Occasionally hyperreflexia and increased tone of the musculature of the lower extremities become evident. Babinski signs may also vanish; however, significant improvement in voluntary motor function of the lower extremities rarely occurs, particularly if the loss at the onset of the illness was severe in character. The degree and manifestations of recovery are variable in any single situation, and, in fact, evidence of return of spinal cord function may never become apparent. Confronted with this situation, the clinician often affixes the label of anterior spinal artery thrombosis to the syndrome, or the vague term "myelitis" is used to designate the clinical state. Suspicion regarding the underlying vascular nature of the lesion should be aroused by the course of clinical events enumerated. However, even though in some instances the circulation of the skin of the lower extremities appears adequate, one or more major peripheral pulses may be found to be absent or greatly diminished. In one patient the only suggestive vascular defect was an absent pulse in one femoral artery. In situations such as these, abdominal aortography will confirm the underlying vascular basis of the spinal cord disease by disclosing occlusion of the distal abdominal aorta. At the present time six such instances have been encountered.

ILLUSTRATIVE CASES

1. *Rheumatic Heart Disease, Auricular Fibrillation, Sudden Onset of Paralysis of the Lower Extremities with Evidence of Dysfunction of the Distal Spinal Cord. Absence of Gangrene. Absent Pulses in the Lower Extremities. Proven Aortic Occlusion by Aortogram and Operation.*

J. P., white male, aged 37 years, was admitted to the hospital because of the sudden onset of excruciating pain in the low back and lower extremities with "numbness and paralysis" of the lower limbs. During the preceding 15 years, recurrent difficulties related to rheumatic heart disease had been present. One year prior to entry into the hospital, transient hemiparesis had been evident on the right side for five hours. Nine days before hospitalization, following stretching in bed, severe lancinating pain appeared in the right lower quadrant of the abdomen and in the right flank. Cystoscopic examination did not disclose a suspected calculus in the urinary tract. Pain persisted until one week later when, following a bowel movement, excruciating pain occurred in the low back with radiation into both lower extremities. At this time the lower limbs could not be moved and were "numb". Urination was possible. Upon admission to the hospital one day later, pain was intense; the left lateral decubitus position was preferred, with hyperextension of the back. Attempts by the examiner to move the patient only evoked responses indicating severe pain, and the lower limbs were held flexed at the hips and knee joints. Rectal temperature was 100.6. The rhythm of the radial pulse was grossly irregular, with a rate of 120. The respiratory rate was 24. The arterial blood pressure was 140/90, while auscultation of the heart disclosed auricular fibrillation. The remaining abnormal pertinent physical features were confined to the lower limbs and trunk. Both lower extremities were warm. Good capillary and venous filling was demonstrated, even though the normal arterial pulsations of all vessels in both lower limbs were absent. In the right groin a cordlike structure, presumed to be a thrombosed femoral artery, was present, and abdominal aortic pulsations could not be felt below the midabdominal area. Marked spasticity was present in the lower extremities. The hamstring muscles were taut and voluntary motor function

A B

Fig. 1. Roentgenograms demonstrate pantopaque in the spinal subarachnoid space from myelography which did not disclose a lesion. Superimposed aortogram demonstrates (arrow) absence of filling of the distal abdominal aorta immediately after injection of opaque material and twenty seconds later. In the later roentgenogram (B) collateral filling of the vessels to the lower extremities is evident.

was absent. All muscle reflexes in the lower extremities were absent. The lower superficial abdominal reflexes and cremasteric reflexes were also absent, but minimal abdominal musculature responses were obtained after stroking the skin of the upper abdomen bilaterally. There was no response to plantar stimulation. Proprioceptive sensibility was absent in both lower extremities and appreciation of pin prick was markedly reduced in the right lower extremity up to the knee and on the left side to the groin. Analgesia was present over the entire posterior aspect of both lower limbs, but the saddle area and genitalia retained normal sensation. Roentgenograms of the chest disclosed a "mitral configuration" of the heart, and roentgenographic examination of the thoracolumbar spine did not disclose any abnormality. Calcification was not demonstrated in the abdominal aorta. The cellular content of the peripheral blood was normal. Urinalysis disclosed albuminuria. On lumbar puncture the spinal fluid was found to be clear and manifested no cellular or chemical abnormalities. Serological examination of blood and spinal fluid gave normal results. A spinal subarachnoid block could not be established by appropriate methods. In the following two days, pain decreased remarkably. "Pins and needles" appeared in both lower extremities and analgesic areas were now found to be hypalgesic. Proprioceptive sensibility remained markedly disturbed. Movement was beginning to return to the right leg. Three days later, the skin temperature of the right and left foot decreased and the distal parts of the lower limbs became pale; paralysis again returned to the right lower extremity. Appreciation of pin prick was now disturbed to just below the costal margin bilaterally. Superficial abdominal reflexes were not obtained and muscle reflexes were still absent in the lower extremities. There were no sphincteric difficulties. Gradually some voluntary movement returned to the right lower extremity and finally to the left lower extremity, the most marked paresis being present in the distal parts. An aortogram disclosed occlusion of the distal abdominal aorta (Figure 1, A and B). This finding was subsequently verified at operation, at which time a thrombo-endarterectomy (Figure 2) was performed. This procedure did not have any effect on the neurological syndrome. There was never evidence of gangrene. The last examination several months later disclosed some improved motor function in both lower extremities. Muscle reflexes in the lower extremities remained absent, but the superficial abdominal reflexes had returned to normal status in the upper quadrants of the

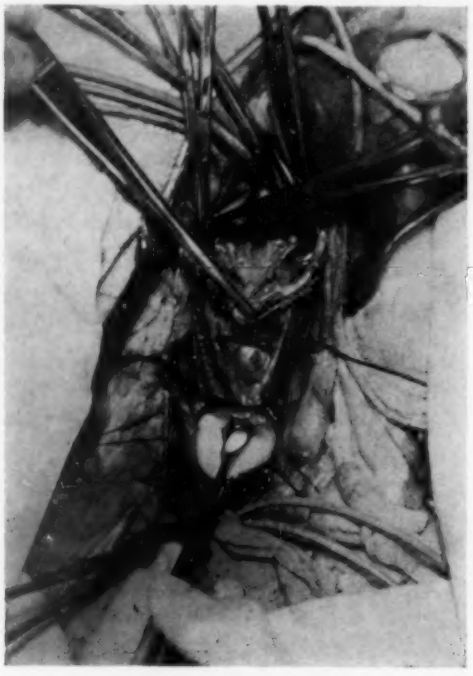

Fig. 2. Photograph taken at the time of thrombo-endarterectomy of the abdominal aorta (Case 1).

abdomen. Hypalgesia was still present to just below the costal margin, although normal sensation was preserved over the saddle area.

Comment

The neurological features in this patient indicated a lower motor neuron lesion as well as a tract lesion affecting the distal spinal cord. The subtending factor was lodgment of an embolus at the bifurcation of the distal abdominal aorta with impairment of circulation to the spinal cord, presumably through one of the radicular arteries. Temporary amelioration was followed by more cephalad extension of the abnormal neurological features. This may have resulted from propaga-

Fig. 3. Abdominal aortography indicating occlusion of the abdominal aorta (Case 2). Evidence of previous laminectomy is seen.

tion of a thrombus proximally. Of particular significance is the fact that occlusion of the distal abdominal aorta was manifested clinically solely by the neurological syndrome as outlined, without significant alteration of the skin circulation of the lower extremities.

2. *Sudden Onset of Bladder and Anal Sphincteric Incontinence. Mild Paraparesis. Laminectomy did not Disclose an Obvious Intradural Lesion. Gradual Amelioration of Neurological Symptoms in the Lower Limbs. Persistent Sphincteric Inadequacy. Aortogram Demonstrated Occlusion of the Distal Aorta.*

M. L., a middle-aged female, was able to recount the following history when examined some four years after the initial onset of her difficulty. She was in good health when she awoke one morning to find a puddle of urine in her bed. A physician was consulted immediately. It was observed at this time, however, that walking was somewhat difficult. Cystoscopy was performed and allegedly there was no reason disclosed for the urinary difficulty except a "weak bladder". Following cystoscopy incontinence of feces was observed. Neurological examination was performed at this time. The patient stated that there was numbness to pin prick up to the level of the midabdominal area. Walking was still possible but increasingly difficult. A myelogram failed to disclose evidence of a block, and a lumbar laminectomy also failed to disclose the etiology of the total bladder and anal sphincteric incontinence. Some two years later the problem was again reviewed neurologically. Hypalgesia was observed to the level of the knees bilaterally. Muscle reflexes were absent in the lower extremities. Approximately one year later, at the time of our examination, sphincteric incontinence remained total. There was vague hypalgesia over both legs and feet. The Babinski sign was present on the left but not on the right side. Motor power in both lower extremities was good. Both knee jerks were present. Ankle jerks were still absent. Proprioception was intact. Because of suspicion of aortic occlusion as the basis for this syndrome, aortogram was performed. This disclosed total obstruction of the abdominal aorta at the level of L_2-L_3 vertebrae (Figure 3).

Comment

The clinical history of rapid onset of symptoms referable to the spinal cord and the neurological pattern described by the patient with subsequent improvement aroused suspicion of a vascular lesion in the spinal cord. For this reason, the aortic lesion was disclosed by aortography.

Discussion

Vascular disease of the spinal cord occupies a curious position in neurological doctrine in that it is acknowledged almost only by the denial of its existence. Clinically, the sudden appearance of symptomatology and signs referable to the spinal cord is often considered in the vague category of "myelitis". Yet, if a clinical syndrome of the spinal

cord is classified under vascular disease, the anterior spinal artery is almost universally designated as the site of the disease process and the label "anterior spinal artery syndrome" firmly affixed. Acceptance of such notions has perhaps prevented the more frequent reporting of the syndrome described.

In 1911 Dejerine[1] described a condition which may be intimately related to the type of vascular disease of the spinal cord in the patients under consideration. Reichert, Rytand and Bruck[2] (1934), in fact, thought that such a syndrome was related to atherosclerosis. In their patients there was heaviness and weakness of both lower extremities, appearing and becoming intense during exercise, with relief following a period of rest. There were no signs of vascular insufficiency in the lower limbs, and the neurological abnormalities consisted of a mixed upper and lower motor neuron type of disorder. Mention was not made of the possible role of disease of the abdominal aorta at this time but it was felt by Dejerine that the basic disturbance was intermittent insufficiency of the circulation of the spinal cord. In 1925 Hunt and Cornwall[3] reported two instances of paraplegia associated with thrombosis of the distal abdominal aorta, and Hirsch[4] described an instance of myelomalacia associated with aortic occlusion. Apparently, these are the only verified reported instances of spontaneous occlusion of the abdominal aorta, manifested clinically primarily by a spinal cord syndrome, and without the so-called usual signs of vascular insufficiency in the lower limbs. In spontaneous dissection of the aorta, in which there are clinically recognizable signs of spinal cord dysfunction, the resultant clinical features are dependent upon the level of dissection in the aorta and the number of successive radicular arteries implicated. In our own experience, as well as that of others, instances have been encountered of dissection of the abdominal aorta where the significant late residua have been varying degrees of dysfunction of the spinal cord, but originally, vascular changes of fairly marked nature had been present in the lower limbs. This is in contrast to the patients considered here, in which there is little suggestion at all of the underlying vascular basis of the spinal cord dysfunction, except from the mode of onset and possibly the change in the peripheral pulses, but without significant circulatory embarrassment in the lower limbs. In the group of patients under consideration, the spinal cord dysfunction is always referable to the lower spinal cord segments and does not extend cephalad above the

Fig. 4. Photomicrograph showing necrosis of the spinal cord of patient with occlusion of the abdominal aorta with the clinical syndrome of only dysfunction of the spinal cord.

eighth dermatomic zone. There is also evidence of lower motor neuron disease referable to these lower segments. The constancy of this pattern makes it evident that the radicular artery or arteries from the lower aorta are implicated. Aortography in these situations will often show the underlying vascular basis of the syndrome. It is of importance to note, however, that spontaneous occlusion of the distal abdominal aorta alone will not ordinarily result in the syndrome described. The demonstration of the occlusion of the abdominal aorta simply provides ground for speculation that a similar process has affected the segmental radicular arteries regionally as well as proximal to the occluding lesion, resulting in necrosis of the spinal cord (Figure 4).

Summary and Conclusions

A syndrome manifested primarily by dysfunction of the spinal cord but associated with occlusion of the abdominal aorta without the usual circulatory change in the lower extremities is described. The precise clinical characteristics observed warrant the utilization of aortography to establish the underlying vascular basis of the disease. Mention is made of other syndromes whose misinterpretation in the past has permitted the present entity to be generally unrecognized.

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REPORT ON AIR POLLUTION AND HEALTH*

The Health Effects of Community Air Pollution: An Assessment

BY THE

COMMITTEE ON PUBLIC HEALTH**
THE NEW YORK ACADEMY OF MEDICINE

Since the air around us is an indispensable element in our existence, its purity is naturally of grave moment. However, a distinction must be made between impairment of health and other consequences of the contamination of air. Although concern over the health aspects of air contamination arises from potential danger to physical wellbeing, concern over the esthetic and economic aspects is more widely evident. Certainly the soiling and deterioration produced by polluted air are both offensive and costly. Nearly every city dweller has had personal experience with odors and eye irritation from polluted air and can testify to the importance of this annoyance for him. Significant though this is, however, there is no evidence that odors and eye irritation result in permanent impairment of health.

Increased contamination of the air has in general followed technological development and increased density of population. Although this trend is natural it is not inevitable, and it is hoped that practical control procedures will become available. Modern civilization has added new sources of air contaminants to the old ones. There are now many contributors: industries of a wide variety; public agencies which operate burning dumps, incinerators, and power plants; and the individual citizen who makes a not inconsiderable contribution through the burning of fuel and waste as well as with his automobile, which is becoming an important source of air pollution.

Although the economic and nuisance liabilities of polluted air are readily apparent and demonstrable, the situation with respect to the

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graver question of a menace to health is more complicated. This complexity arises from a series of circumstances. 1) The health effects either demonstrated or suspected (for example, respiratory disorders and lung cancer) are for the most part not uniquely the consequence of air pollution but are with us, though possibly in lesser degree, whether or not the air is polluted. 2) They may develop in a subtle and slowly progressing manner and are accordingly difficult to detect. 3) Objective answers in many instances will be based on careful statistico-medical studies, which are only now being put under way, and on studies of exposure of individuals to various concentrations of sulfur dioxide in the atmosphere.

There is no generally accepted evidence at this time that air pollution, for the larger part of our population, is a major contributor to ill health in comparison to the generally recognized causes of disease. However, it has been demonstrated that air pollution, though not a major factor, may be of significant health concern.

1) There is unquestioned evidence that in restricted localities a potential health menace of disaster proportions may develop when extreme pollution is aided by unusual meteorological and topographic conditions. An example is the Donora episode of 1948 which led to 20 deaths. Fortunately the coincidental circumstances required are such that the likelihood of occurrences of this kind, though real, is low.

2) There have been suggestions that certain industrial effluents (for example, beryllium) have in special cases led to difficulty in the immediate vicinity of industrial plants, and that other more generally present trace contaminants might produce still undefined illnesses; these, either because of the local nature of the problem or because of present vagueness, are deemed at this time of lesser urgency than the following issues.

3) Statistical evidence, though still meager, is consistent with the possibility that an increased incidence of lung cancer is associated with city air pollution. Carcinogenic materials have been found as air contaminants. Examination of the evidence would suggest that air pollution is not the only, nor even the major, factor in lung cancer. It may, however, be a significant one; only additional information can resolve the question.

4) A number of air contaminants of cities, such as sulfur dioxide and ozone, are lung irritants and over long periods can produce

demonstrable lung damage, or more acutely, place additional stress on the respiratory system and heart of persons already ill of asthma, other respiratory diseases, heart disease and related conditions. The concentrations required to provoke effects that can be easily detected are in general well above those found in even our most heavily polluted cities. However, in New York City both in 1955 and 1957, the Commissioner of Air Pollution Control, Dr. Leonard Greenburg, has reported concentrations as high as those which were found in London smog. It is not an unreasonable inference that prevalent concentrations of these irritants may produce definite health effects. Since polluted air can be only one of a number of contributing stresses in these disorders, it is to be expected that though these effects may well be of real public health importance, they will be difficult to assess with quantitative certainty.

In summary, therefore, it can be said that unusual circumstances of meteorology and terrain could conceivably lead to a local acute air pollution episode. Of greater general significance, urban air pollution, though probably not a major source of disease, may be a significant contributor to chronic disease in the case of lung cancer and possibly as an additional burden for those with respiratory and cardiac disease. There is growing evidence to support the former while the latter is still largely inferential.

These circumstances point urgently to the need for additional studies to permit more accurate answers to the questions imprecisely answered here. Although there are large areas of uncertainty, the conclusions just summarized are of sufficient weight to support vigorous corrective efforts. The present situation is not good; if nothing is done it will inevitably become worse. Practical control procedures need to be made effective through better operating procedures and engineering improvements. These will need to be ensured by appropriate regulation and encouraged by education of the public.

AIR POLLUTION AND HEALTH

A REVIEW*

ALVAN L. BARACH

Air pollution, long recognized as a menace to health and comfort, is increasing in our urban and industrial communities at a rate which makes it one of our most urgent environmental problems[1]. The ventilation limit of many of our cities—their ability to dispose harmlessly of poisonous gases, soot particles, and fly ash into the upper atmospheric trash-basket—has already been approached. Every new power plant, smoke-stack, refinery, home furnace, incinerator, automobile, bus or truck adds to the burden, and during the next decade or so these sources of contamination will increase by at least 25 per cent. For air pollution is a disease of increasing population[2], and it has been estimated that by 1975 there will be in America alone 55,000,000 more persons to be serviced by means of devices that will produce air pollution.

The financial burden of air pollution is already staggering. Crop damage in the Los Angeles area in 1957 was estimated at $5,000,000[3, 4]; the deterioration of stone buildings and the corrosion of metals and paint[5], directly traceable to air pollution, play a large role in every city budget. "It is estimated conservatively that the cost of air pollution to the citizens of the City of New York is approximately $12 per person per year, or $100,000,000", according to the Department of Air Pollution[6]. The chemical industry was recently reported as spending $40,000,000 yearly and the automotive industry is said to have devoted $5,000,000[8] in so far unsuccessful attempts to develop oxidizers or afterburners which will eliminate the harmful hydrocarbons in gasoline and diesel motor exhausts.

There are few cities in the United States of over 25,000 population without some form of air pollution control[7]. In 1955, after President Eisenhower, in his State of the Union address, called attention to the growing menace, Congress authorized the appropriation of $5,000,000

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a year for five years to provide aid to state and local government air pollution control agencies as well as to other public and private agencies, institutions, and individuals for research, training, and demonstration projects. In addition, the Federal Government was authorized to enter into contracts for similar purposes with public and private agencies, institutions, and individuals[9].

The greatest motivating force behind all this activity is, of course, concern for human health. The effects of air pollution on human health range from discomfort, depression, and irritation of the eyes and throat to loss of workdays, bronchospasm, chronic illness, and death.

How widespread and serious are these effects? More and more responsible investigators are now devoting themselves to the evaluation of this problem. Already available—and as yet little known to the general public—is considerable evidence linking air pollution to the increased incidence of chronic bronchitis, emphysema, and lung cancer in urban and industrial areas. Is there then an effect of continuous, low-grade exposure—particularly on such large groups in the population as the very young and the aged, the allergic, and those with respiratory and cardiac impairment? And what is its role apart from the known seriousness of smog "incidents", when concentrations of pollutants in the air reach lethal proportions?

1. Smog "Crises"

The chief source of air pollution is the burning of fuels of all kinds. For example, the equivalent of 32,000,000 tons of coal (the figure includes fuel oil and natural gas) is burned in New York yearly. Since about 5 per cent of the weight of the coal and oil used in New York City passes into the air as sulfur dioxide, it is calculated that over 1,500,000 tons of sulfur dioxide are poured into the surrounding atmosphere every year[10].

In Los Angeles County 2,500,000 registered automobiles use 4,600,000 gallons of gasoline per day, and of this total 7 per cent is poured unconsumed into the atmosphere every day[11]. Most of the time (when the weather is favorable) the resulting air pollution does not exceed the so-called "tolerance" level presently used. But it is well known that only the interference of the weather—low pressure areas or periods of inversion (a warm blanket of air above a colder one)—is required to precipitate real crises.

One of these crises was a five-day fog in London in 1952, which became a national catastrophe. During this period some 4,000 deaths occurred in London[12]. Only the peak week of influenza in November 1918 produced more deaths over an expected normal mortality, and the cholera epidemic of 1866 did not equal it[12]. It is somewhat startling to find that during recent years concentrations of SO_2 as high as that found in the London catastrophe, namely, 1.34 ppm., have on occasion been reported in New York City[6, 12].

Smog in Los Angeles was responsible for 281 excess deaths from cardiac and respiratory disease in the last 137 days of 1953, and 334 such deaths in 1954, according to Mills[13]. In the latter year there was one episode when an inversion ceiling of 900 feet persisted for 21 days[14]. Mills commented: "There exists no longer a reasonable doubt that Los Angeles smogs are indeed related to very considerable increases in respiratory and cardiac deaths."

Reporting on an analysis of the daily mortality experience among Los Angeles residents since 1954, Breslow and Goldsmith[15] of the California State Department of Public Health find no clear association between any single episode of air pollution and excess mortality, and do not support Mills'[13] claim of 334 excess deaths in 1954. They state, however, that while no definite effect on mortality from air pollution alone has been ascertained, this is not to say that no such effect occurs. In their opinion, the question requires continuing study:

> "The possibility of a lethal effect from air pollution deserves attention in all metropolitan areas. Eastern cities of this country suffer in varying degree from air pollution caused by combustion of coal, the discharge of waste from factories, and other sources. The fact that Los Angeles has attracted the greatest public attention is no reason for other areas to be complacent.
>
> "The air we breathe is not subject to individual control in the same sense that other aspects of the environment may be controlled. Without warning it may affect the frail and the infirm, and with present technology, once air pollution has occurred, little can be done to protect the many susceptibles."

Breslow and Goldsmith also report that in a representative statewide sampling of the population of California in 1956, about two-fifths of the adults in 3,545 households stated that they were bothered by air pollution. In Los Angeles County the proportion was two thirds, in other parts of the state about one-fifth.

Some of the effects were described as follows:

> "Most persons complained about eye irritation, with nasal symptoms next in frequency. Typical responses were: 'My eyes water and it's hard to breathe and sometimes I get a headache.' . . . 'Physically, it bothers hayfever and sinuses—eye irritation. Shortens temper and gives a bleak mental outlook.' "

"Furthermore", the report continues, "the adults in one out of eight Los Angeles households reported that they are now considering a change of residence because of air pollution; others considered changing jobs."

A survey conducted by the Smog Committee of the Los Angeles County Medical Association in 1957[14] shows irritation of the eyes and the respiratory tract, pain in the chest, cough, dyspnea and nausea as symptoms of smog poisoning or the "smog syndrome". A large percentage of physicians believed that patients with respiratory diseases were more susceptible to smog than healthy adults; 68.1 per cent believed that patients with cardiac disease were more susceptible. Patients thought to be particularly susceptible were the aged and those with allergies or anxiety states. Atmospheric concentrations of ozone above 0.2 ppm. irritated the air passages and resulted in progressive, cumulative damage, particularly in the elderly and in persons with bronchopulmonary or cardiac disease[13].

Nelson[16] has commented: ". . . a nonspecific respiratory irritant or group of irritants impose an additional stress on an already overburdened respiratory or cardiac system". In another paper[17], he describes the mechanism as follows:

> ". . . in a person with a pre-existing lung or circulatory disease, this usual safety factor has disappeared and no reserve is available to meet the challenge of the new stress. In this case, the congestion and increased permeability of the capillary walls arising from the irritant effect of inhaled material can lead to progressive fluid accumulation, that is, pulmonary edema. This, in turn, interferes with the oxygen uptake, which then adds the vicious cycle, since a lack of oxygen favors increased fluid effusion. If there is a heart or circulatory difficulty, the lung changes add to this pre-existing burden an additional one arising from the impediment to ready circulation through the lungs. There is ample documentation of the effect of pre-existing lung or heart difficulties on the increased susceptibility to air pollutants. Table I, adapted from the Public Health report on the Donora episode, illustrates the enhanced sensitivity of persons with heart or lung difficulties."

TABLE I. INCIDENCE OF SMOG AFFECTION IN DONORA AS INFLUENCED BY PRE-EXISTING DISORDERS

Group	Per cent with Smog Affections	
	All degrees	Severe
Average		
All persons	42.7	10.4
Pre-existing		
Bronchial asthma	87.6	56.6
Heart disease	77.2	36.5
Chronic bronchitis	78.9	26.8

The dramatic Donora episode, to which Nelson referred in the preceding quotation, has provided some clinical evidence about acute air pollution sickness. In 1948 a four-day smog which settled over Donora, Pennsylvania, produced respiratory symptoms, pain in the abdomen, splitting headache, vomiting, and some coughing up of blood. As shown in the preceding Table, taken from a study made at the time by the U.S. Public Health Service[18], 42.7 per cent of the population of Donora, or 13,000 persons, were affected in some degree by the smog. Twenty deaths occurred.

In 1957 a follow-up study[19] of the group of 4,092 persons who were included in the original study indicated some of the long-term effects of exposure to smog. Information was obtained on all but 41 of the original group; 314 were reported to have died.

The major finding that emerged from the study was that "persons who were reported ill in 1948 at the time of the smog episode have demonstrated subsequently higher mortality and prevalence of illness than the other persons living in the community at that time. Furthermore, persons who complained of more severe illness in 1948 demonstrate greater subsequent morbidity and mortality than persons with mild complaints".

The analysis showed that the greater morbidity and mortality were apparently related to the cardiorespiratory system.

In addition to the comparison of those affected by the smog with others in the community who were not affected, the follow-up study included comparisons of mortality rates in Donora with the rates in Washington County, the State of Pennsylvania, and the United States.

Donora's average annual mortality rate in the period 1948-1957 was shown to be roughly the same as the rate in Washington County, and

somewhat less than the 1954 and 1956 rates for the State of Pennsylvania. Using the mortality rates for the United States for the period 1949-1951, the investigators found that "the only conclusion that seems warranted is that during the period 1948-1957 the mortality experience of the Donora sample was not strikingly different from that of the United States".

As to morbidity, the survivors of the affected group were shown to have a higher frequency of current illness and a higher prevalence of chronic illness than the survivors of the "not affected" group. They were particularly prone to heart disease, asthma, and bronchitis.

2. Effect on Incidence of Bronchitis and Lung Cancer

Additionally significant is the mounting evidence of a relationship between increasing death rates from cancer of the lung and certain materials in urban atmospheres which have been shown to be carcinogenic.

In Great Britain investigators have demonstrated that both mortality from chronic bronchitis and incidence of the disease are higher in urban communities which have greater amounts of air pollution than in rural areas[20, 21]. These findings may be summed up in the following quotation from Dr. John Pemberton[22], Director of the Medical Research Council for Epidemiological Research in Respiratory Disease, and Reader in the Department of Social and Industrial Medicine, University of Sheffield:

> "The long term effect of air pollution on health has been examined by comparing the bronchitis death rates with the average amount of air pollution in the county boroughs. This study showed a significant correlation between the average level of sulphur dioxide pollution and the bronchitis death rate in men over the age of 45. Daly [*Brit. M. J. 2*:687, 1954] found a similar relationship between bronchitis rates and the amount of domestic coal burned.
>
> "The effect of air pollution on sufferers from chronic bronchitis has also been studied by asking patients with this condition to keep diaries in which they record whether they are in their usual health or whether they are worse. It has been found that there is a sudden increase in the numbers reporting themselves worse when there is a marked increase in air pollution."

A number of British workers during the past 20 years have demonstrated differences between the death rates from cancer of the lung in town and country. Stocks[23], in a study of regional and local differences in cancer death rates published in 1947, showed that the rates for cancer

of the lung were far lower in rural areas than the rates in London and other large cities. He also correlated the lung cancer death rates with hours of sunshine, and concluded that "either smokiness of atmosphere is an important factor in itself in producing cancer of the lung, or sunshine is an important factor in preventing its incidence".

In a recent report of a study of the possible influence of both smoking and air pollution on cancer of the lung, based on statistics for two years, Stocks and Campbell[24] state that the concentration of benzpyrene in the air of Liverpool was from 8 to 11 times as high as the concentration in the rural areas examined, a ratio which corresponded with the estimated mortality ratio among non-smokers living in the areas studied.

Official British Empire Cancer Campaign findings for 1955[25] indicate that ". . . the urban-rural ratio of lung cancer deaths amongst non-smokers is about 9 to 1, and corresponds roughly with the ratio between the concentrations of 3:4 benzpyrene, some other polycyclic carbons and sulphur dioxide found in the air of the city and the concentrations found in rural situations".

Kotin and his associates at the University of Southern California School of Medicine have carried out a series of investigations of the effect of polluted air on mice. In 1954 they reported[26] that they had succeeded in inducing skin tumors on mice by painting the skin with a benzene solution of extracts of natural smog. Two years later they reported[27] the appearance of pulmonary tumors in 80 per cent of mice of A strain exposed to ozonized gasoline in an inhalation chamber for 52 weeks. Among controls in a chamber containing washed air, 41 per cent developed lung tumors. In a third paper[28] the group reported a similar study in which they used test mice of a strain highly resistant to tumors ($C_{57}BL$). After 92 weeks, lung tumors appeared in two and one-half times as many mice in the "smog chamber" as in the mice in washed air.

In the survey among the members of the Los Angeles County Medical Association[14] in 1957, slightly more than half (50.7 per cent) of the physicians who responded expressed the opinion that smog is a contributing factor in cancer of the lungs and air passages. Of the remainder, 42.2 per cent said they had no opinion, and 7.1 per cent thought that smog had no effect.

The American Cancer Society, in its recent study of the smoking habits of nearly 188,000 men in relation to cancer of the lung, found

that the death rate was lower in rural areas than the rate in cities: 39 per hundred thousand in the country as compared with 52 per hundred thousand in cities. Hammond and Horn[29], in their report on the study, comment:

> "This difference may be due to some factor producing lung cancer with city life or to better case finding and diagnosis in cities than in rural areas."

Further statistical evidence of the difference between urban and rural mortality from lung cancer appears in a study of the geographic distribution of mortality from this disease in the United States. Hoffman and Gilliam[30] presented mortality rates adjusted for urban and rural residence by age, race and sex. In all age groups and in both white and nonwhite persons the rate in urban areas exceeded that in the rural population. In many instances the urban rate was double that in rural areas. These authors did not comment on possible explanations for the differences in rates. They observed that:

> "It is not possible with data presently available here or elsewhere to determine whether they are due to occupational, environmental, economic, diagnostic, or other factors, although there has been considerable speculation regarding reasons for such differences."

That the recent increases in the occurrence of lung cancer are related to the development of modern industry has been attested by a number of investigators, chief among them, perhaps, Dr. W. C. Hueper of the National Cancer Institute[31], who has declared:

> "The widespread presence of industry-related atmospheric pollutants of recognized carcinogenic properties suggests that the recent alarming rise in lung cancer frequency especially among males may in part be causally related to the local and general development of modern industry and the use of its products."

In a Public Health Monograph, Hueper[32] points out that "a real, definite and progressive increase in the frequency of lung cancer started in most industrialized countries around the turn of the century, that is, at a time when cigarette smoking was still a habit of minor significance".

Mills[33], reporting a study in Cincinnati of tobacco smoking, motor exhaust fumes, and general air pollution in relation to the incidence of lung cancer, stated that exposure to motor exhaust fumes and general urban air pollution greatly increased the hazard of lung cancer in smokers.

Shimkin and Shope[34] recently reported that investigators in the U.S.S.R. have noted increasing mortality from lung cancer in their own industrial areas and have attributed it to air pollution.

Kuru[35] of Osaka University Hospital is said to have stated that in his opinion modern skyscrapers contribute to the rise in lung cancer. He believed that the vertical concentration of people added to pollution of the air and in addition the buildings act as traps to prevent polluted air from being dispersed.

3. Effect on Normal Persons

Two out of five people interviewed in the statewide survey in California covering adults in 3,545 households said they were bothered by air pollution, according to Breslow and Goldsmith[15]. To this subjective evidence from the general public is being added a growing volume of scientific data showing that irritation of the eyes and throat and alterations in pulmonary function have been produced experimentally by concentrations of irritants ordinarily considered safe. Such effects, indeed, have been found in subjects exposed to concentrations below the level of sensory detection.

In 1953 Amdur, Melvin and Drinker[36] at Harvard University showed that inhalation of sulfur dioxide in low concentrations (1 to 8 ppm.), below the sensory threshold (that is, below the level at which they could be detected by smell or actual sense of irritation), produced consistent changes in respiration and pulse rate. Breathing became shallower and more rapid; pulse rate increased, and tidal volume decreased in normal subjects. Nelson[17] has commented on these experiments as follows:

> "These results are among the first to show that levels of these pollutants approaching those found as general air contaminants can in fact produce demonstrable functional changes in man. Since the subjects did not know that they were receiving contaminated air, these effects must necessarily be involuntary physiological responses."

Lawther[37], reporting similar experiments, said that he had not been able to confirm the findings of Amdur and her co-workers.

Sim and Pattle[38] also exposed normal subjects to sulfur dioxide, sulfuric acid mist, and various aldehydes, and recorded evidence of increased airway resistance and the production of râles with rhinorrhea and lacrimation. Two subjects developed bronchitic symptoms that

lasted ten months. The addition of steam, enlarging the size of the particles, increased the irritant effect. Those exposed by the use of masks to sulfur dioxide in strengths from 1.34 to 80 ppm. reacted with varying degrees of bronchoconstriction and sibilant râles in the chest; coughing and some bronchoconstriction and râles followed exposure in a chamber to 0.7-9.6 ppm. of dry sulfuric acid (10 N, 1 micron diameter). Pattle and Cullumbine [39] in 1956 showed that increase in particle size in sulfuric acid mist increased its toxicity.

A number of investigators have observed that seemingly unrelated factors, such as a combination of pollutants in the air at low concentrations, varying amounts of water vapor, and sunlight combine to produce by a synergistic action effects not associated with exposure to a single contaminant[16, 38, 40, 42]. Concentrations can be below those generally considered harmful—even below the conscious threshold—yet there will be damage to physical and mental well-being[15-17].

New York City's Department of Air Pollution Control carries on its publications for distribution to the public the slogan "Clean Air Means Better Health for All", and its director has said unequivocally that "any unbiased review of the literature must lead one to conclude that there is a definite connection between the health of a community and the amount of air pollution in that community"[43].

Along with the health factors already discussed, and over and above the physical costs of the depredations of grime, the loss of sunlight, and the presence of sulfur dioxide, the effects on the mental health of a community are considerable. An editorial in the New York State Journal of Medicine[44] expresses the view that "Only when every man, woman and child realizes the danger to health and wellbeing which air pollution causes will we be on the road to controlling the problem . . . reducing the danger and the nuisance which face all of us".

4. Principal Air Pollutants

The first reported death from air pollution is perhaps that of Pliny the Elder, who succumbed to pollutants in the air following the eruption of Vesuvius in 79 A.D. It is interesting that Tacitus records that Pliny had previously suffered from bronchial disease. Early records of man-made pollution go back over 600 years to the introduction of the use of coal in London; and as early as 1306 a Londoner was not only arrested but tried and executed for transgressing what was perhaps the

first anti-air-pollution ordinance. John Evelyn, the diarist, 300 years later, in 1661, described the effects of air pollution in London as follows:

> "And what is all this, but the Hellish and Dismall Cloud of Sea-Coale? which is not only perpetually imminent over her head . . . but so universally mixed with her otherwise wholesome and excellent Aer, that her inhabitants breathe nothing but an impure and thick mist, accompanied by a fulginous and filthy vapor . . . corrupting the Lungs and disordering the entire habit of their bodies; so that Catarrs, Phthisicks, Coughs and Consumptions rage more in this one City than in the whole Earth besides."[22]

a. *Sulfur Dioxide.* Investigators have identified the principal villain in the piece as sulfur dioxide, given off as a by-product of combustion of industrial and domestic fuels, of petroleum refining, and of the incineration of garbage. Held in the soft, spongy particles of soot, it is readily oxidized into dilute sulfurous and sulfuric acid. In Greater New York, an average of 67.7 tons of soot per square mile fell each month in 1957, though the concentration in Manhattan proper averaged 102 tons per square mile per month[6].

Sulfur dioxide is "invisible, has a characteristic sharp odor, irritates the nose and throat at levels of around 15 parts per million or more and is irrespirable at about 100 parts per million (or 0.01 per cent by volume), but is detectable by most persons at about 1.5 parts per million. Green plants begin to show burning by sulfur dioxide in concentrations upwards of 0.25 parts per million—long before man is bothered"[2]. Investigators at New York University report that while 0.5 parts per million can injure plant life, 2 parts per million can annoy human beings[45].

Thomas[46] in the United States studied the effects of sulfur dioxide on plants, particularly the visible yellow leaf lesion which is accompanied by a failure of growth. Bleasdale[47] in Manchester compared the growth of rye grass in two greenhouses. One received ordinary Manchester air, while the other received only air from which the smoke and sulfur dioxide had been removed. He found that there was a failure of growth in the first greenhouse even when the concentration of sulfur dioxide was insufficient to cause a yellow leaf lesion.

The New York City Department of Air Pollution Control[6] reported that in 1956 the average concentration of sulfur dioxide in the air in the city as a whole was 0.21, with a maximum of 1.28. In 1957 the average was 0.20 and the maximum was 1.40. In a survey made by the Interstate

Sanitation Commission of New York, New Jersey and Connecticut, concentrations of 2.0 and 2.08 were recorded during the first seven months of 1957, with concentrations of 1.2 even at the top of the Belvedere Tower in the center of Manhattan's Central Park[5].

Particle size, solubility, a combination of two or more irritating substances, combination of irritant gases with toxic metals, sun, heat and humidity may all increase the danger potential. The greatest damage inflicted by sulfur dioxide is to the bronchi, with erosion of the lining epithelium, submucosal edema, and thrombosis of small arteries and veins. Workers exposed to high levels of sulfur dioxide in manufacturing plants show a high incidence of chronic catarrh, emphysema, inflammation, shortness of breath, and fatigability.

b. *Ozone.* Along with sulfur dioxide, a chief gaseous offender in the air of such cities as New York[5] and Los Angeles is the ozone which results from the photochemical oxidation of hydrocarbons present as a result of the partial combustion of gasoline and diesel fuel. This has been demonstrated by Haagen-Smit[42] at the California Institute of Technology. Hydrocarbons present in exhaust fumes from motor vehicles, when acted on by sunlight in the presence of nitrogen oxides which are also released in the processes of combustion, produce ozone and other oxidation products, which even in low concentrations may cause the cracking of rubber[42] and paint[5] and the disintegration of nylon stockings[43], and may be toxic to plants and human beings.

Went[3] reports that peroxides and ozonides present in 0.01 ppm. cause silvering and browning of plant-leaves, and that at 0.2 ppm. this injury becomes severe. The growth rate of seedlings in the Los Angeles area is said to have been reduced one-half by air pollution.

Atmospheric concentrations of ozone above 0.2 ppm. irritate the bodily air passages of persons, causing pain in the chest, cough, dyspnea and nausea. When concentrations of 0.5 ppm. are reached in Los Angeles, a "smog alert" is called, halting all but the most necessary traffic, but Thienes[48] has recently presented evidence that levels of more than 0.1 ppm. for more than four hours are probably hazardous.

c. *Carcinogenic Substances.* The 3,4-benzpyrene and other polycyclic hydrocarbons known to be carcinogenic have been found in soot and fly ash, and they are also present as a result of the photochemical oxidation of hydrocarbons in motor vehicle exhausts. As has been said, evidence from varied and reputable sources here and abroad which

links the increase in death rates from lung cancer among urban males to the pollutant material in the air of cities cannot be dismissed. The following is from the 1954 Annual Report of the British Empire Cancer Campaign[49]:

> "The approximate amounts of benzpyrene inhaled by town dwellers, and by smokers, can now be estimated. If a person smokes 40 cigarettes a day for a year the smoke produced will contain about 150 mg. of benzpyrene, and in a large town the air inspired during the same time might contain 200 mg."

The biological activity of soot entering the respiratory tract favors the development of cancer of the lung, according to Hans Falk and his co-workers[50], at the University of Southern California School of Medicine. In a study of the effect of cellular and plasma proteins on the evolution of benzpyrene from soot, they concluded that the plasma protein in the lungs dissolves 3,4-benzpyrene out of particles of soot, leaving the carcinogen free to be acted upon by lung tissue to form cancer.

d. *Radioactive Materials.* The most recent contaminants of the atmosphere, those arising from the use of nuclear energy, may menace the survival of the human species itself. H. G. Baity, Director of the Division of Environmental Sanitation of the World Health Organization[51], has observed:

> "This is a very special aspect of air pollution at present handled by departments of the atomic energy organizations of the various countries. It is apparent, however, that with the development of nuclear energy for industrial purposes, the whole subject of the dispersal, monitoring and control of radioactive effluents cannot remain divorced from the problem of air pollution in general."

5. What Can Be Done

The primary attack upon air pollution lies in the development of chemical and engineering methods to improve combustion and reduce the particulates in stack gases, in fly ash, and in motor exhaust gases. Meanwhile, government regulation and enforcement, and a vigorous campaign to enlist public support and understanding can help to prevent avoidable pollution. Progress in methods of sampling, and the many long-term studies, now under way, of the complicated factors involved, promise to add to the knowledge with which we may hope to combat the rising tide in the future.

Experience during smog incidents has indicated some methods of

protection. The similarity of the effects of the London smog of 1952 to a mild gas attack led to the use of simple masks or respirators[2]. It was found that remaining indoors and inactive was helpful to older people, especially to those with bronchitis, asthma, and coronary artery disease[12]. Certain patients were advised to use carbon filters in air conditioners or masks in sickrooms; others used wet gunny-sacking over window openings.

A suggestion that dust from cement works may be protective against atmospheric pollutants has recently come from Dr. J. H. Hudson[52] of Dartford, England, who has reported that the incidence of lung cancer in the cement district was markedly lower than that in Greater London, its immediate neighbor. Dr. Hudson noted that "at the central London power station sulphur dioxide is removed from the flue gases by chalk and lime". He concludes: "Is it not possible that in the cement districts the chalk and lime suspended in the air is diverting the acid oxides of sulphur, and thereby preventing their harmful partnership with smoke particles? The freedom from acid and the high sulphate content of our deposit gauge readings seem to fit in with such a picture."

Ammonia has also been found helpful, according to Sim and Pattle[38], Parker[20], and others. Sim and Pattle report that dispersion of ammonia in the chamber after subjects had been exposed to acid mists reduced both irritation and bronchoconstriction. Magnesium oxide was equally effective. Parker reports that 100 patients with bronchitis in Great Britain have tried equipment for emitting ammonia into the air in suitable quantity, with what seem to be beneficial results. He also mentions a kind of cravat, incorporating a controlled source of ammonia, which has been developed so that it can be worn near the mouth by people working out of doors during periods of smog.

Drinker[2] sums up the evidence for ammonia thus:

> "It was reported at the time of London's severe fog that the prize cattle at the Smithfield show were badly affected but that ordinary cattle for slaughter were not. The prize animals were kept clean, and their stalls were clean. The ordinary ones, on the other hand, stood in the familiar aroma of the barnyard in which ammonia is commonly in fair concentrations. This ammonia, it was assumed, neutralized both the sulphur dioxide gas and sulphuric acid mist.
>
> "Carrying this idea a step farther, it is suggested by Wilkins [*Brit. M. J.* 2:1135, 1955] in London that an adjustable wick dipped into a bottle of ammonia serves as 'an elegant alternative to an indwelling pig'. A report

> is also given of the effectiveness of a damp baby, something no mere engineer would venture to suggest."

At the WHO-sponsored Geneva conference held in 1958, air pollution was recognized as the greatest and most urgent environmental problem facing the peoples of Europe[51]. In America, not only the government, but industry, engineering, and medicine are concerned, and great strides are being made in establishing regulations for smoke control, in sampling, and in setting up long-term statistical studies.

Long-term studies on the effects of exposure of normal individuals to atmospheres containing low-level concentrations of pollutants have been initiated by Federal, State, and local groups, as well as by individual scientists. These studies, along with proper evaluation of morbidity and mortality statistics, will take many years. Meanwhile, Hitchcock[4] declares: "We at the Air Pollution Foundation . . . begin by making the assumption that smog is bad in general, that it is not wise to wait 10 or 20 years to see if smog is convicted medically."

"This country has not had any incident to compare with London's", comments Professor Drinker[2]. "But it would be folly not to take the eye-smarting in Los Angeles and in the New York City and New Jersey areas as warnings and heed them."

Finally, the speakers at recent conferences on air pollution expressed their beliefs unequivocally that chronic air pollution induces serious biological effects in various clinical entities:

At the recent National Conference on Air Pollution sponsored by the Public Health Service*, Surgeon General Burney[54] stated that "after several years of closer observation, investigators are finding a definite association between community air pollution and high mortality rates due to cancer of the respiratory tract . . .".

Leake[55] reported that "in addition to eye and respiratory irritation, the increasing incidence of lung cancer is quite as referable to increased city auto traffic exhausts as to cigarettes".

Kotin[56] concluded that atmospheric pollution, "in and by itself, uniquely supplies the links necessary for the experimental induction of lung cancer. In the absence of evidence or data to the contrary, this observation coupled with the epidemiological characteristics of the disease strongly suggests a similar action for man".

Mancuso[57], reporting that "the native white male mortality rate for

* Nov. 18-20, 1958, Washington, D. C.

lung cancer is over 100 per cent greater in urban areas than in rural areas," makes this statement: "The evidence of an 'urban' factor for lung cancer distinct from smoking patterns, or questions of classification or diagnosis, appears to be secure."

Wilson and Farber[58] reported a definite relation between the smog or air pollution level and the aggravation of the symptoms of 45 patients with pulmonary emphysema living in San Francisco*.

A similar relation was reported by Carey[59] in England in cases of chronic bronchitis, some of whom presumably may also have had pulmonary emphysema.

The review that has been presented amply justifies the writer's conclusions.

Conclusions

The tragic toll of death when the polluted air of industrial communities is raised to lethal concentrations by natural phenomena constitutes a plain and simple warning of what can occur. Evidence is also mounting of the deleterious effects of day-to-day exposure to even lower concentrations. Continued exposure to air pollutants has been repeatedly linked with the increasing urban incidence rates of bronchitis and other lung diseases, including lung cancer.

It is clear that sulfur dioxide and other irritants in the air are poorly tolerated, particularly by the elderly and by those who already suffer from some form of respiratory or cardiac disorder.

So far, this disease of civilization is outstripping all efforts to cure it. In spite of what is being done, the trend is still upward, as industrialization and population increase.

* Paper presented at Air Pollution Conference of State Department of Public Health, San Francisco, Jan. 1959.

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THE USE AND ABUSE OF IRON THERAPY AND TRANSFUSION

*Transcription of a Panel Meeting on Therapeutics**

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MODERATOR CARL H. SMITH: The subject of today's meeting is *The Use and Abuse of Iron Therapy and Transfusion.* In reviewing the history of transfusions, I found the following description of this form of treatment in the writings of Libavius in 1615 which I thought very timely:

> "Let there be a young man, robust, full of spirituous blood and, also, an old man, thin, emaciated, his strength exhausted, hardly able to retain his own soul. Let the performer of the operation have two silver tubes fitting into each other. Let him open the artery of the young man and put into it one of the tubes, fastening it in. Let him immediately after open the artery of the old man and put the female tube into it, and then the two tubes being joined together the spirituous blood of the young man will pour into the old one as if it were from a fountain of life, and all of his weakness will be dispelled."*

As far as I could discover, this is the first reference for the treatment of "tired blood"!

The earlier treatment with iron, too, was often symbolic and mystic, with the implication that iron was indicative of strength and was imbued with some strange fuel by Mars. It seemed logical that a condition characterized by weakness, such as anemia, should be treated with a remedy suggesting power and strength.

These references are made to underscore the thesis that in an era in which iron kinetics and metabolic changes in the red cells are meticulously investigated in health and disease, both iron and blood are so frequently employed indiscriminately. The emphasis on the benefits of trace elements to re-enforce iron and in correcting iron deficiency anemia has become an area in which confusion exists. The increased availability of blood has also led to a sharp rise in the number of transfusions, often beyond the need for relating them to correcting a predetermined physiologic need.

The program of this panel is extremely timely, namely, to provide a forum in which the uses and abuses, the indications and contraindications, the benefits, and the hazards of both iron medication and blood transfusions can be discussed. We are fortunate to have as members of

* Kilduffe, R. A. and DeBakey, M. The Blood Bank and the Technique and Therapeutics of Transfusions. P. 18. C. V. Mosby Co., 1942.

this panel experts in this field, so that the therapeutic, experimental and pathological aspects may be evaluated and integrated. After brief presentations by the members, the remainder of this session will be conducted informally with questions from the floor and from the members of the panel among themselves.

I shall now introduce the members of the panel. Dr. Louis R. Wasserman will discuss "Iron Metabolism and the Indications for Iron Administration and the Use of Parenteral Iron". Dr. R. Janet Watson will discuss "The Use and Abuse of Transfusions". Dr. Paul Reznikoff will discuss "The Role of Trace Elements, the Abuse of Iron Therapy, and the Problem of Multiple Deficiencies". Finally, Dr. John T. Ellis will present "The Pathology of Iron Excess; the Current Concepts of Hematochromatosis".

Dr. Wasserman, will you open the discussion?

DR. LOUIS R. WASSERMAN: The total amount of iron in the body is relatively small; approximately 4.5 gm. of iron, about 70 per cent of which is present in the form of hemoglobin, serves a most important role as an oxygen carrier, entering directly into many key metabolic processes.

Iron in food exists as hemoglobin, which has recently been shown to serve as a source of dietary iron, various other iron-protein complexes and inorganic iron salts, both ferric and ferrous. Peas, beans, dried fruits, egg yolk, nuts, wheat germ, liver and heart are among the richest dietary sources of iron. Ferrous iron is more readily absorbed than ferric iron. This imposes two conditions on the food iron that is to be absorbed, first, that any ferric iron present be reduced to the ferrous form and second, that this ferrous iron be absorbed at a pH less than 6, since above this pH both ferrous and ferric ions alike form insoluble complexes.

In the stomach, the gastric acidity aids in the dissociation and solution of the various iron complexes present in food. Together with the natural reducing substances present in food it provides the proper pH for the reduction of ferric iron to the ferrous form.

Absorption of iron takes place primarily in the upper portion of the small intestine, particularly the duodenum, where pH conditions are most favorable. Peak serum iron levels occur about 2 to 5 hours after the oral administration of iron.

Only a small part of the dietary iron intake, less than 10 per cent in

normals, is absorbed, but this is sufficient to keep an individual in a positive balance of 1 mg. of iron per day. The remainder of the iron is excreted in the feces, within 24 hours after ingestion. This is essentially the only method the body possesses for the elimination of iron, since iron once absorbed is retained in the body, save for a small quantity that is excreted in the bile and a negligible amount in the urine.

The various factors controlling iron absorption are poorly understood. The level of the blood iron, the level of the plasma iron-binding protein and the extent of the body iron stores have been shown to have no influence on the amount of iron absorbed. The oxygen content of the blood, however, is believed to play some role in controlling the avidity of the body for iron.

Iron is absorbed directly into the portal system, the lymphatics having relatively little role in iron absorption. Experimental studies, chiefly by Granick, have further elucidated the method of absorption and have demonstrated the presence of a protein, apoferritin, which appears in the cells of the gastric and duodenal mucosa in response to iron feeding, and which can combine with iron to form a new compound, ferritin. Ferritin is an iron-protein compound (molecular weight 460,000) that contains approximately 17 to 23 per cent of iron. The iron in ferritin is in the ferric form and may be removed from this protein by reducing agents, without denaturation of the protein. According to Granick two mechanisms take part in regulating iron absorption in the mucosal cell. The first is the mechanism of the "mucosal block", i.e., the gastrointestinal mucosal cells adjust their uptake of iron according to their level of saturation with an iron compound. This is related directly or indirectly to the ferritin content of the mucosal cell. The second mechanism is connected with the "redox" level of the cell in which the reducing systems act to convert the ferric hydroxide micelles to ferrous iron, the ferrous iron then diffusing into the blood stream. As stated previously, in anemic conditions the lower oxygen content in the mucosal cells would favor this reduction. Under normal conditions, ferritin would begin to be stored in response to the ingestion of iron and the block to further iron absorption would be established.

The mode by which iron is taken up and transported in the blood stream has recently received considerable attention. The normal concentration of the serum iron varies from 75 to 150 gamma per 100 ml. This is present in the ferric form and is carried by a specific protein,

beta-l-globulin (also known as transferrin or siderophilin), found in fraction IV-7, and is present in a concentration of approximately 0.27 gm. per 100 ml. Ferrous iron as it is released from the intestine is believed to be auto-oxidized to the ferric form and in the presence of carbon dioxide, combined with beta-l-globulin to form the iron protein compound.

Normally the beta-l-globulin is only one third saturated with iron, i.e., the serum is capable of binding a total of 250-350 gamma of iron per 100 ml. This last figure is termed the serum iron-binding capacity and may be determined by means of either *in vivo* or *in vitro* tests.

The turnover of this plasma iron has been shown by radioiron techniques to be an index of erythropoiesis. Radioactive ferric citrate is incubated with a purified fraction of beta-l-globulin and injected intravenously. The disappearance of the radioactivity varies in different bone marrow functional states. In aplastic anemia the rate is slow, in hemolytic anemia it is rapid.

Following the expiration of the red cell's normal life span the erythrocyte is destroyed and the iron it contains once more becomes available for further use by the body. Twenty-seven milligrams of iron are released daily, representing the breakdown of approximately 8.1 gm. of hemoglobin per day. An equal amount of iron obviously is needed for red cell synthesis if a constant equilibrium is to be maintained. However, of this 27 mg. only 70 per cent can be utilized for hemoglobin synthesis (this being the relative proportion of hemoglobin iron to the total body iron, assuming a similar turnover rate for all the body iron). The remainder of the iron needed for red cell regeneration will have to come therefore from the diet or the body iron stores. Only a fraction of the storage iron, however, is available to the active metabolic pool.

With this brief outline of iron metabolism, the normal daily requirements may be considered, and what effect aberrations of this source have in the etiology of iron deficiency. The daily recommended intake of iron is 12 mg. in the food, for both men and women. In adolescence, pregnancy and lactation, the recommendation is raised to 15 mg. daily. For infants the suggested dietary allowance is 1 mg. per kg., for children it is 0.6 mg. per kg. Looking at this somewhat differently, in the case of adults if one assumes that 70 per cent of the iron in the food in an average diet is available and only 10 per cent of this fraction is assim-

ilated, then a diet containing 15 mg. of iron will give 1 mg. daily absorption.

Iron deficiency anemia is the most common deficiency state.

There are several causes for iron deficiency anemia. In general it can be stated that this type of anemia, in the absence of pathological blood loss, is most likely to appear in infancy and childhood with equal frequency in both sexes; in puberty and adulthood, more commonly in females, and also during pregnancy.

The treatment of iron deficiency anemia is a specific one, namely the administration of iron. Alteration of the dietary intake is usually insufficient in cases that have progressed to the frank development of iron deficiency anemia. It is not necessary to give any additional erythropoietic factors, such as liver or any of the vitamins or minerals, nor is the addition of hydrochloric acid necessary. The mode of administration is almost always by the oral route and while there are a number of proprietary preparations available, ordinary ferrous sulfate is most satisfactory. Iron is usually administered between meals to reduce the incidence of gastric irritation. Again it should be mentioned that the greater the amount of dietary bulk and phosphate content the less the absorption of iron. Tolerance for iron salts is usually achieved by giving a small dose at first and gradually increasing the amount. With the suggested scheme of dosage a reticulocyte response is usually seen within three days, reaching a peak between 5 to 10 days, its magnitude usually being inversely related to the pretreatment concentration of hemoglobin. Hemoglobin regeneration takes place in a characteristic manner. There is at first a lag of several days until the peak of the reticulocyte increase is reached, following which the hemoglobin value rises at an average rate of 0.15 to 0.25 gm. per 100 ml. daily.

There is rarely any indication for parenteral iron therapy, especially in view of the hazards usually associated with this form of therapy. Until recently there was no safe or satisfactory preparation for intravenous or intramuscular use. This is due to the fact that preparations of iron with ionic iron given intravenously in excess of the serum iron-binding capacity leave the blood stream rapidly, with resultant toxic symptoms such as flushing, diaphoresis, palpitations, abdominal cramps, nausea, vomiting, diarrhea, shock and even death.

Preparations of saccharated iron oxide are now available for intravenous use and if cautiously administered have none of the side effects

formerly observed. A more useful parenteral preparation in our hands has been the iron-dextran compound that is given intramuscularly. The exact amount to be given must be calculated so as to avoid oversaturating the tissues, since with the intravenous or intramuscular route one is bypassing the intestinal barrier, which normally regulates the intake of iron.

The rare indications for such parenteral iron therapy include gastric lesions (such as ulcer and gastritis) in which the iron may act as a further irritant, cases of ileitis and colitis (in which the increased gastrointestinal mobility would make for decreased absorption of iron), pernicious vomiting of pregnancy and those unusual instances of defective iron absorption.

MODERATOR SMITH: Dr. Watson, would you continue this discussion?

DR. R. JANET WATSON: I should like to talk about the indications and contraindications for transfusion therapy in anemia. The indications, of course, will depend on the circumstances causing the anemia. In acute blood loss, obviously, blood needs to be replaced, and in acute blood loss the level of the hemoglobin will not be the deciding factor because it takes 24 to 48 hours for hemodilution to take place to show the true hemoglobin, so that the amount of blood given by transfusion will often depend on the clinical history and estimation of how much blood the patient has lost.

Then, another problem about transfusions is in the case of anemias in which there is a specific therapy, such as iron in iron deficiency anemia and B_{12} in pernicious anemia. Under what circumstances do these patients require supplementary blood transfusions? It is usually not necessary to give any blood unless, as in pernicious anemia, the red cells fall as low as one million per cmm. with signs of incipient heart failure, in which case it may be necessary to give a small blood transfusion to tide the patient over until the time that vitamin B_{12} takes effect. But, if the patient with one million red cells is perfectly comfortable, with a normal pulse rate, and with no infection, it may be quite safe to withhold transfusion.

The same holds true of iron deficiency anemia. Many patients with hemoglobins as low as two and three grams per cent may be fairly comfortable, and because of the rapid response to iron therapy, transfusion will not be required. But, again, if there are signs of incipient heart failure, a temporary blood transfusion may be necessary. In such

cases, it is better to give packed red cells in order not to overload the heart with excessive fluid volume. The blood should be given very slowly over a period of several hours. As far as the total amount is concerned, most adults can tolerate either 500 ml. of whole blood or 250 ml. of packed red cells. In children, the amount of whole blood is usually based on 20 ml. per kilogram or 10 ml. per pound of body weight; and, again, if packed cells are being given, one may use half these amounts or something in between.

Another type of anemia, such as an acute hemolytic anemia, which has developed very suddenly so that the hemoglobin has fallen, for instance, from 15 grams to 9 grams per cent in 24 hours (equivalent to the loss of one-third of the blood volume), will produce symptoms of acute blood loss and will require immediate blood replacement. However, if the patient has had a chronic hemolytic anemia for many weeks or months, that is quite a different situation. Cooley's anemia, sickle cell anemia and aplastic anemia are common examples of anemias that are chronic and provide the patient with a chance to become adjusted to a low hemoglobin. Empirical experience in dealing with these patients indicates that they will be quite active and have very few symptoms until the hemoglobin falls somewhat below 7 grams per cent, certainly below 6 grams per cent. In our clinic, for example, our indication for transfusing a patient with Cooley's anemia or sickle cell anemia is usually a hemoglobin of 6 grams per cent, or below. This is because at about that level the patients will begin to develop fatiguability on exertion, loss of appetite and irritability.

In chronic anemias, such as sickle cell anemia, in which it is found that a patient can stabilize at a certain hemoglobin level, say 7 or 8 grams per cent, for month after month, transfusing these patients to higher levels of hemoglobin does not make them more comfortable or more active, and is a waste of blood. In sickle cell anemia, a great many patients stabilize their hemoglobin values above 7 grams per cent and do not require transfusion more than once a year, many not at all,—although there are certain exceptions in which there is complicating hypersplenism. In contrast, in Cooley's anemia, there is a rather constant downward trend of hemoglobin, so that if no blood is given, the hemoglobin will fall to levels as low as two or three grams per cent. Here again, it is found that if the hemoglobin is maintained by frequent transfusions at high levels, such as 11 and 12 grams per cent, the patients

do not derive much clinical benefit, but on the contrary, may succumb sooner to the complication of hemosiderosis. The best thing therefore is to transfuse patients only for symptoms when the hemoglobin level reaches approximately 6 grams per cent.

In general, these comments fit other diseases in which anemia may be present. For instance, in leukemia, if the hemoglobin falls to a point where there are symptoms present, it will be important to transfuse. The same holds in chronic nephritis with a severe anemia.

And, again, symptoms also will depend on the activity of the patient. If he is a day laborer who works hard eight hours a day, it may be necessary to transfuse him at a higher level than a person who stays home all day and has little or no physical activity. So, there are many individual considerations other than just the hemoglobin level.

In general, whole blood is the easiest type of blood to use. But, if one wants to put in a lot of red cells and raise the hemoglobin as high as possible, one can give, instead of two separate transfusions of whole blood, a single transfusion of packed blood cells. Again, decisions of that sort will depend on how much blood one wants to give a particular type of patient.

The contraindications for transfusion include the fact that transfusion reactions due to mismatched blood do occur even in the best blood banks. There will be an occasional death due to transfusion of the wrong type of blood. There are other types of reactions also. If the blood is given without any real indication for it and a transfusion death results, this would be, of course, disastrous for the patient.

Furthermore, Dr. Smith, along with some others, has shown that giving a large volume of blood will suppress blood formation. For example, if a patient with sickle cell anemia is given 1000 ml. of blood, the reticulocytes, which were originally high, will fall to a low level, and the patient's ability to make red cells is suppressed. This is an additional reason for restricting the amount of blood given to certain patients.

Finally, in patients who have chronic anemias, such as the aplastic and Cooley's types, and who require frequent transfusions throughout their lives, death will eventually occur due to hemosiderosis. If the transfusions are kept to a minimum this complication will be postponed. Further comments will be left to Dr. Ellis, who will discuss the subject in more detail.

MODERATOR SMITH: Dr. Reznikoff, will you continue?

DR. PAUL REZNIKOFF: I have been asked to speak principally about the abuse of iron therapy, either because I am qualified in the field of abuse or in that of iron therapy, I am not sure which.

If we start with the perfectly valid assumption that Dr. Wasserman has made, that the only indication for iron therapy is iron deficiency, then we might state categorically that the use of iron for anemia not due to iron deficiency is an abuse of iron therapy. We may go further and point out that any anemia is due to some cause and is not a disease in itself; it is only a sign of a disease. Therefore, the use of iron without trying to find out the cause of the anemia is not only an abuse but indicates a poor quality of medical practice.

For example, consider a patient who has anemia, and whose doctor prescribes iron. After some months the patient is found not to have responded very well or only slightly. It is then discovered that he has anemia because he is bleeding from a carcinoma of the cecum which might have been discovered months sooner. This is not only abuse but is really malpractice.

One question that practitioners frequently ask the hematologist is this: "Why can't we use iron as a psychological remedy?" Well, that depends on the taste. I would rather prescribe a cocktail. However, the physician should not fool *himself* but realize what he is doing.

What are the real dangers of excessive iron therapy or iron therapy over a long period of time? Dr. Watson mentioned these. Hemosiderosis may develop, just as it does with excessive numbers of transfusions, and hemosiderosis, which may not be a dangerous condition, may develop into hemochromatosis, which is a disease. Dr. Ellis will discuss this presently.

Dr. Wasserman mentioned the use of parenteral iron. It should be remembered that parenteral iron must be given very carefully. It has been reported that with iron dextran one may get skin discoloration, which is not pleasant for the patient; and if you give intravenous iron and don't get it into the vein, you can produce local necrosis and, under certain conditions, thrombosis.

In connection with iron therapy, the question arises as to whether it is necessary to have certain adjuvants which Dr. Wasserman mentioned, such as copper. Isn't it true, you might ask, that you might increase the efficacy of iron therapy with these heavy metals? Well, we know quite

well that in humans and, certainly, in adults, we have enough of these trace metals, such as copper, in the normal diet to provide the necessary amounts that are required to convert iron into hemoglobin. So, from a practical standpoint, there is never any indication to add them to our remedies, and it is not good scientific practice and not good practical medicine to add traces of these metals to iron, increasing the cost of the medication.

An old hematologist once stated that if a patient needs iron, he can eat the iron bar of a fence and he will get enough iron. That is a little difficult to do. But, what he meant to imply was that you did not have to get very fancy about your treatment.

Dr. Wasserman pointed out that it is necessary for ferric iron to be converted to ferrous iron; and then the question arises whether ascorbic acid added to iron might not aid this. That may be so from a theoretical standpoint; but I would like to point out that patients with achlorhydria, and not taking ascorbic acid, did rather well with ferric salts even though, theoretically, the conversion of the iron was not quite as efficient. However, when we prescribe iron we usually give so much that the stools are always black; therefore, we know that, as a rule, we are giving much more than is necessary.

The question of using hydrochloric acid, however, is an interesting one, because if hydrochloric acid were essential for the conversion of ferric to ferrous iron, all our pernicious anemia patients should be iron deficient, and they are not. So, a good deal of iron can be absorbed or converted without hydrochloric acid being present in the gastric contents.

There are patients with a type of anemia which is associated with thyroid insufficiency and occasionally such a patient will have microcytic anemia. In those cases, the adjuvant is not really an adjuvant but is a remedy, that is, thyroid substance which has to be given with iron. Another question which also comes up frequently concerns the use of folic acid as an adjuvant. Is there any evidence that folic acid increases the effectiveness of iron therapy? I think there is very good evidence that it does not,—that an iron deficient patient can get along quite as well with just iron provided the patient's anemia is due to iron deficiency alone. There are patients, of course, who have multiple deficiencies. Those patients will not only need iron but will need B_{12} or folic acid, and proteins, and so forth. But, such conditions are good indications not

for a shotgun remedy but for supplying the patient with what is needed because of multiple deficiencies due to dietary defects. I have seen such patients, as probably most of you have, during pregnancy.

In general, you might say that no therapy should be used, unless there is an emergency, which will obscure the diagnosis of the disease. If you have a patient with anemia and prescribe iron, B_{12} or folic acid, and then find the anemia improved, and you then try to determine whether it is a microcytic or macrocytic anemia, you will be stymied. Therefore, a diagnosis of the type of anemia, with some indication of the cause, should be made before giving the patient any remedy. That is very simple. As a rule, all that must be done is a red blood cell count, a hemoglobin determination, a white blood cell count and differential, and hematocrit. That takes only a short time. Then, if you must give a remedy, even in an emergency, you usually have the basis for a diagnosis.

Dr. Watson correctly pointed out that only anoxia is the indication for transfusion; and she also pointed out what should be emphasized—that anoxia depends not only on the degree of anemia but on the rate of formation or development of the anemia.

It is true that a patient may not be anoxic lying quietly in bed before an operation, but the surgeon knows that unless the blood count is brought to a certain level the patient will become anoxic. There is, therefore, a justification for giving transfusions to patients with anemia if the blood count is too low; and this holds true in obstetrics. The late Dr. Pastore demonstrated that the incidence of postpartum infection has a relationship to anemia before delivery.

MODERATOR SMITH: I note that the speakers have mentioned hemosiderosis and hemochromatosis when discussing the results of the abuse of transfusions and iron therapy. Our final speaker, Dr. Ellis, is well qualified to discuss these subjects. I am sure that in the presentation he will point out the difference between hemosiderosis and hemochromatosis, and how these terms apply to transfusion therapy and to iron medication.

DR. JOHN T. ELLIS: During the last several years we have had the opportunity of studying liver specimens from 28 cases of Cooley's anemia, procured either at the time of splenectomy or at postmortem. These patients have been followed clinically for prolonged intervals of time and offer a wonderful opportunity to study many of the problems associated with the accumulation of iron pigments in human tissue.

The first slide demonstrates that the amount of iron which can be found in the tissues of chronically anemic patients given multiple transfusions greatly exceeds that which is contained in the transfused blood. For example, in this case we recovered 13 grams of iron in the liver, and one gram of iron in the pancreas and heart, yielding a total of 14 grams, whereas the patient had received only 6.6 grams of iron from the transfused blood. The other two cases are similar. These observations indicate that patients with severe chronic anemia, who have huge accumulations of iron in the tissues, continue to absorb excessive quantities of iron by way of the gastrointestinal tract.

(Slide) This slide indicates that whether we speak of hemosiderosis or hemochromatosis these conditions are more complicated than just the accumulation of iron pigment in various tissues. For example, note that the amount of iron contained in 100 grams of dry tissue in Case No. 2 was 1600 milligrams, the normal being 50 milligrams. In addition, lead was increased some 50 times normal; copper was increased five times normal; the aluminum values were lower than normal, and calcium was increased greatly. Increased amounts of various trace metals is not specific for Cooley's anemia, but has been reported in many other types of chronic anemia and in idiopathic hemochromatoses as well. In general, when iron values are markedly elevated, the lead, copper, molybdenum values are also high. The significance of the increase in the other trace metals is uncertain but it seems likely that these findings may be of importance.

(Slide) In the human, when iron stores increase, a brown coloration of the tissues appears in the heart, liver, spleen, pancreas, adrenal, thyroid and salivary glands. For the most part, such accumulations of iron pigment are not accompanied by demonstrable functional alterations.

(Slide) The findings in the hearts of patients with Cooley's anemia and excessive stores of iron are of great interest and importance. Four patients who received multiple transfusions died in heart failure and had had abnormal cardiac rhythms. The relationship, if any, of the cardiac siderosis to the functional change is unknown.

Iron pigment also accumulates in the endocrine glands but we do not know what effect this has on the functioning of these tissues. Perhaps the increased melanin in the skin and the failure to grow normally after puberty is in some way related to the accumulation of iron in the endocrine glands.

In the pancreas, the iron accumulates largely in the acinar cells and in the beta cells of the islets of Langerhans. In only two of the patients whom we have studied has there been evidence of functional alterations. One of these patients developed a frank diabetes mellitus, and another showed an abnormal glucose tolerance curve.

In the liver of many of these patients a fine cirrhosis develops, in addition to the brown discoloration caused by the iron pigmentation. None of these patients has shown abnormal liver function tests.

It also should be pointed out that the amount of iron *per se* could not be closely correlated with the amount of hepatic fibrosis. For example, one patient received 49 grams of iron contained in the blood received by transfusion, this being the equivalent of 98 liters of blood, and yet had only minimal cirrhosis. On the other hand, another patient who received only 0.5 gm. of iron, or that contained in one liter of blood, showed a great deal of fibrosis.

The distinction between hemosiderosis and idiopathic hemochromatosis usually offers no difficulty. In idiopathic hemochromatosis the absorption of iron from the intestinal tract is increased in the absence of anemia. In hemosiderosis, on the other hand, there is usually chronic anemia requiring repeated transfusions. Iron absorption from the intestinal tract is also increased. In hemosiderosis, it is not usual to have clinical signs of cirrhosis or diabetes mellitus, whereas these are common in the late stages of idiopathic hemochromatosis.

However, it should be mentioned that, in rare instances, cases of chronic anemia may develop findings that are indistinguishable from classical hemochromatosis.

MODERATOR SMITH: *There are questions that have been submitted,—some from the audience. Before we turn these over to the panel, may I ask this question: Dr. Ellis, is there any harm, physiologically, from the deposition of iron in tissues, if the iron does not invariably precede or accompany hemochromatosis?*

DR. ELLIS: The basic question as to whether iron is injurious to human cells has not definitely been answered. For example, one can give large amounts of iron to experimental animals, and the iron accumulates in various cells; but as far as one can tell, it does no damage. In other words, in experimental animals the accumulation of iron in the liver is not accompanied by demonstrable functional abnormalities, and does not lead to cirrhosis of the liver. In humans, the siderosis and cirrhosis usually

co-exist. But, whether they are causally related or are merely parallel phenomena, has not been decided as yet, in my opinion.

MODERATOR SMITH: *I should like to ask Dr. Wasserman whether he considers that the administration of iron is harmful in individuals who have infections. Will the iron be absorbed? Is the administration of iron harmful in hemolytic diseases?*

DR. WASSERMAN: If the iron is not given in excessive amounts, I don't think it can be harmful. If it is given in excessive amounts, however, I believe that iron is harmful, and I think has occasionally even caused death. I am thinking particularly of those cases of hemosiderosis associated with massive transfusion therapy where these patients die of cardiac failure. We have had this experience, also, in many of our patients who have had aplastic anemias or myofibrosis where we wish to do splenectomies. In our series of cases, of which incidentally, only one has survived, most died of cardiac failure; and we ascribe this to a deposition of iron in the heart muscle.

MODERATOR SMITH: *I have another question: Dr. Watson, do you consider overwhelming infection an indication for fresh blood transfusion?*

DR. WATSON: I would, if anemia is present. But if the hemoglobin is 13 grams or more, I would not give the blood. In the presence of an overwhelming sepsis, I would transfuse at a much higher level of hemoglobin than I would ordinarily. For instance, I would give a transfusion of whole blood to a patient with a mild iron deficiency who also had a severe sepsis, even though in the absence of sepsis such a patient would not ordinarily be transfused. I think this is a controversial point. I wonder if other members of the panel might have something to say about it.

DR. REZNIKOFF: I, too, think it is a controversial point. I am still of the opinion that, considering the danger of transfusion reactions, hepatitis, and so forth, the same criteria ought to hold in overwhelming infections as in a non-infected individual.

Transfusions used to be given for infections by some of our older clinicians because it was believed that normal blood contained some protective bodies that might help combat the infection. But we must remember that transfusions may not only cause immediate damage but may also cause other damage, hepatitis, etc. Therefore, in a patient with a mild anemia I would be opposed to giving a transfusion, whether the patient was infected or not.

MODERATOR SMITH: *Dr. Reznikoff, do you think that in a patient with acute loss of blood, preliminary digitalization is necessary; and, secondly, would you bring the hemoglobin level up to normal? In other words, should enough blood be given to bring the hemoglobin up to 15 or 16 grams, or would 11 grams suffice?*

DR. REZNIKOFF: I don't think this question can be answered adequately because I don't think a patient ought to be treated according to a number or according to a chart. The patient ought to be treated in relation to his specific blood requirements. I certainly wouldn't digitalize a patient if the cause of the cardiac disturbance or inefficiency were simply due to hypoxia; I would give the patient blood. I don't think that digitalis would be indicated in that case and, in my opinion, I don't think digitalis would do any good. I would give the treatment which would help the myocardium.

MODERATOR SMITH: *Dr. Watson, do you think digitalis is of any value when there is acute blood loss?*

DR. WATSON: No, I don't.

MODERATOR SMITH: *In children, we sometimes digitalize when the venous pressure is high. Isn't that an indication for digitalization?*

DR. WATSON: In that case, with a high venous pressure, there is evidence of heart failure which would be an indication for digitalization.

MODERATOR SMITH: *Dr. Reznikoff, could I ask you specifically about the use of cobalt as an adjuvant in the treatment of iron deficiency anemia? Is there any condition you can think of in which cobalt therapy is of value?*

DR. REZNIKOFF: Cobalt therapy has been used in refractory anemia, in patients who have uremia, and in patients who have infectious arthritis or rheumatoid arthritis, and there has been some evidence that cobalt itself will produce some hematopoiesis. However, it is my impression, after considering the available data, that the amount of benefit has been negligible. Also, I believe that cobalt is a toxic agent. Therefore, I would hardly think that cobalt would be a remedy of choice, or should be considered. At least, I wouldn't give it.

MODERATOR SMITH: *I would like to ask Dr. Wasserman if he has had any experience with the use of cobalt?*

DR. WASSERMAN: We have used cobalt in the treatment of nephritis. We have used cobalt in many refractory anemias. I must admit that I have not seen any effective response to cobalt therapy in any of the

refractory anemias, including that of uremia. As far as I am concerned, it has no place at all in the treatment of human anemias.

MODERATOR SMITH: Dr. Watson, I think you might tell us something about the toxic effects of cobalt when administered to children.

DR. WATSON: Some of them will develop enlarged thyroids. Also, the children may lose their appetites, which, in the end, will interfere with their nutrition. Have you seen thyroid enlargement, Dr. Smith?

MODERATOR SMITH: No. Following the reports of Kriss and Gross we have abandoned the use of cobalt.

There was some mention made of the use of cobalt in Cooley's anemia. We used it in this condition without evidence of improvement in the anemic condition.

I have another question here. When is transfusion indicated in chronic nephritis? Would you answer that, Dr. Watson?

DR. WATSON: In general, we have used the same criteria that I mentioned before, when the hemoglobin falls below 6-7 grams, we will transfuse. However, if the patient is already in a terminal coma, I think it is probably a futile gesture.

MODERATOR SMITH: *Is there any advantage, Dr. Reznikoff, in administrating blood to a person with chronic nephritis?*

DR. REZNIKOFF: There, again, I think the criterion is what the patient needs. If the patient is hypoxic or has a marked anemia, a transfusion will make him more comfortable and help his anemia. But I don't think transfusions ought to be given simply because the laboratory sheet shows a mild anemia, with the patient lying in bed comfortably.

MODERATOR SMITH: *You don't think there is any danger in giving blood to a patient who has had an acute nephritis?*

DR. REZNIKOFF: There is always some danger in giving blood, the danger of reaction, shut-down of a kidney. I think that is the reason I am so insistent that blood should not be given unless indicated, because giving blood is a dangerous procedure.

MODERATOR SMITH: *Dr. Wasserman, have you any thoughts or experience along that line?*

DR. WASSERMAN: Only in relation to kidney function. Until recently it was believed that when the hemoglobin was low and the patient became very anemic, kidney function decreased and the patient suffered because of that. In those patients who already had impaired kidney function, this diminution in the hemoglobin, with the reduced oxygen-

carrying capacity of the blood, was sufficient to cause difficulty.

In a number of cases, however, where kidney function has been followed very carefully, we were able to demonstrate that the level of hemoglobin had little, if anything, to do with kidney function. One of our patients had a hemoglobin of one and one-half grams for a matter of weeks because she was completely incompatible, and we could not get any blood that was compatible with hers. She was pouring out two and three thousand milliliters of urine a day and her hemoglobin remained, as I said, in the neighborhood of about two grams for more than two weeks.

MODERATOR SMITH: *I wonder which members of the panel have had experience with the use of an iron-dextran preparation. I have a question here: Is the skin discoloration of the dextran injection local or general?*

DR. WASSERMAN: We have been using the Feron iron-dextran for the last three and a half years; that is, the initial preparation we received from the laboratories in England, and the material that has been put out for the last few months by the Lakeside Laboratories here in this country. The skin discoloration is purely a local one, and once you see it, you know that the patient has been getting injections of Imferon. It is brownish-black. It usually does not occur until after the patient has received a number of injections. If one is very careful in giving the injection, and puts sufficient pressure against the injection site so that no blood or iron diffuses outward, then there is a minimal amount of discoloration. Apparently, once this discoloration occurs it is fairly permanent; at least it has been permanent for the last three years. What will happen eventually, I don't know.

DR. WATSON: How many patients have had it?

DR. WASSERMAN: All patients who received over ten injections have discoloration.

MODERATOR SMITH: *Dr. Wasserman, under what circumstances do you prefer the intramuscular injection over the oral administration of iron?*

DR. WASSERMAN: Only in those patients to whom we gave it. I have seen only one case of inability to absorb iron from the gastrointestinal tract. He required parenteral iron. All the other cases had some sort of ulcerative colitis or severe ulcers which prevented their taking iron by mouth.

DR. REZNIKOFF: I would like to ask Dr. Wasserman if he thinks a patient with a gastric ulcer will be upset with oral iron? I have given it, and none of my patients seems to suffer.

DR. WASSERMAN: All I can say is that when we begin iron therapy, we always give the material by mouth, if we possibly can. We always start with the simplest form of iron, which is ferrous sulphate. We don't even give Feosol or any of the other tablets that contain Feosol; we give just plain, ordinary ferrous sulphate. If they can tolerate it, fine; if not, we use the other ferrous irons. If they can tolerate any of these materials, we don't give parenteral iron. There is a small number of patients who can't take it by mouth. These are the only patients who receive the material intramuscularly. I must repeat that these are rare cases which get Imferon by injection.

DR. REZNIKOFF: There is one other condition in which we have used parenteral iron, that is in the case of a patient seen in the last month of pregnancy with an obvious iron deficiency anemia, and there is not time to raise the hemoglobin in a short period of a few weeks. I think those patients develop an increase in hemoglobin more rapidly than those who take it orally. I think its use is justifiable in such a condition.

DR. WATSON: At Kings County Hospital we have found another indication for parenteral iron. Nutritional iron deficiency anemia is very common in that particular social and economic group, in the age range of one to four years. Many times the mother has as many as ten children at home, and when we prescribe iron she never has time to give it to the child. In some cases, also, we have encountered a situation in which the child is a behavior problem, and the mother says she can't force the child to take the iron. In such cases we have found Imferon very useful.

In addition, we are also conducting a study of Imferon to find out how it works in a large group of children with nutritional iron deficiency anemia and we have now used it in about 50 children, with no reactions. In no case have we had any skin discoloration. Because the children are small, a total of about five injections is necessary to bring the hemoglobin up to a normal level, and this takes place in four weeks. These injections can be given either daily or weekly, depending on individual circumstances. However, I agree with everyone on the panel that where the mother will give the patient the iron preparation by mouth there is no necessity for giving it by injection.

MODERATOR SMITH: *May I ask you, Dr. Watson, whether, once you*

have reached a normal level of hemoglobin, you stop iron therapy; or, do you continue iron for a considerable period thereafter?

DR. WATSON: When we are giving oral iron we usually continue it for about a month after the hemoglobin has reached normal, believing that we need some extra for the iron stores. What is your practice?

DR. REZNIKOFF: We do blood counts regularly. If it stays normal, we don't give iron.

Going back to the original proposition,—trying to find out the cause of the anemia. If the patient has varices, it is likely that they will bleed, assuming no operation is performed, and so you probably will have to continue to give iron. The same thing is true with hiatus hernia bleeding. If the patient has been bleeding from hemorrhoids, and is successfully operated upon, we don't give iron. It depends on whether we can correct the cause of the anemia.

DR. WATSON: Our patients are growing children. This is analogous to chronic bleeding. The blood volume expands with growth and extra iron is needed for this. So, after a child has reached a normal hemoglobin at one age, by the time he has become a year older, his hemoglobin may drop again and he may require additional iron. That is why in pediatrics we usually give iron for a few weeks after the hemoglobin has reached normal.

MODERATOR SMITH: I think we are all agreed that giving iron on the basis of pallor is deceptive and that one ought really to determine the hemoglobin level. It is a simple office procedure. We frequently find that iron is administered indiscriminately, often depending on the way the patient looks or the way he feels.

I have one more question. Should folic acid be excluded from vitamin pills?

DR. REZNIKOFF: We are opposed to the inclusion of folic acid and B_{12} in vitamin pills because, at least in our cases, it ruins our only method of making an accurate diagnosis in pernicious anemia. In other words, if a patient has pernicious anemia, and you wish to do a bone marrow study, for example, you are not going to diagnose the condition if he has been taking B_{12} and folic acid. Of course we can do a Schilling test.

We have two kinds of pills in our hospital; those for the doctors who want to give the patient the benefit of all doubts, and these pills contain folic acid and B_{12}; and the other vitamin pills are ordered by the doctors who want to find out the cause of the patient's disorder. We

compromise.

In general, of course, most vitamin pills are unnecessary if a patient has an adequate diet. I think that is a good topic for another panel.

When Dr. Foley returned from a prison camp in Japan, he said that the first call he received was from a lady on Park Avenue who said she wanted a shot of vitamins because she had a social function that night and wanted to be up to it. He said that in the Orient everybody needs vitamins and nobody gets them, whereas here everybody takes vitamins and almost nobody needs them.

MODERATOR SMITH: Since there are no other questions or comments, before we adjourn, I wish to thank the members of the panel for their discussions.

THE FERMENTATION PHASE*

JOHN J. TOOHY, A.M.**

FERMENTATION is as old as life, certainly preceding human life, and yet it is one of the most modern and least understood developments that punctuate the history of the drug house.

Rather than attempt to discuss fermentation technically, I should address myself to the history of our efforts to *control* fermentation and to *use it* for man's health and welfare. I must confess at the outset that I have had a rather lengthy experience with fermentation from the viewpoint of health and welfare—my first-hand knowledge of it having come some forty years ago when, like most college students everywhere before the start of the Twenties, I engaged in a do-it-yourself fermentation program. Muddling through some courses in organic chemistry during the early prohibition days, I found myself singularly popular for my convenient access to an occasional beaker of absolute alcohol that would otherwise go down the drain.

It is little recognized that the use of living organisms to perform chemistry at the behest of man is one of the most vital enterprises in the history of mankind. It has played a part in treating the ailments to which man is vulnerable; it has made his food more palatable; it has preserved his plants and changed his agriculture; it has played a vital role in saving the Western Powers in two wars; and it might be said that Israel was created thanks to the powers of Clostridium acetobutylicum to produce acetone from grain.

The history of man's use of the fermentation process contains interesting scenes from almost every facet of man's endeavor.

No one knows, of course, when man began to use the fermentation process, medically or otherwise. The anthropologists tell us that they have discovered no society in which it was not used. The earliest records that I was able to find are those of the Assyrians about 2,000

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**General Manager, E. R. Squibb & Sons, Division of Olin Mathieson Chemical Corporation, New York, N. Y.

B.C. Certainly, beer was known in the fourth dynasty of the Pharaohs, for there are many references uncovered concerning the malting of barley. Even bread has been found in some of the tombs of ancient Egypt, so we can be certain that fermentation was going to work there.

Microbes indulging in fermentation were first utilized as production workers in the chemical industry and by drug houses which acquired experience that proved so valuable to the development of techniques in antibiotic production. The first biochemical explanation was given by Pasteur. Just a century ago, Louis Pasteur in his "Mémoire sur la fermentation appellée lactique", summarized the experimental evidence which proved that living agents were responsible for the phenomena of fermentation. He attributed the process in which sugar in aqueous solution is decomposed into alcohol and carbon dioxide to the action of yeast cells. Pasteur recognized that, while decomposing the sugar in the absence of air, yeast cells live and propagate in the fermenting liquid, and he called the process of alcoholic fermentation "life without oxygen".

Since about 1893 it had been well known that molds of certain types, *Citromyces*, grown in a cane sugar solution produce citric acid. Commercial fermentation by molds in the United States is founded on work done by Dr. James N. Currie. Dr. Currie had access to a collection of molds built up in the laboratories of the Bureau of Chemistry by Dr. Charles Thom and Dr. C. G. Church. By substituting a strain of *Aspergillus niger* for the *Citromyces*, he got an optimum production of citric with limited production of by-product oxalic acid. Stimulated by the war-time shortage of citric acid, the process evolved into commercial operation at the Pfizer Laboratories.

We all know that it was Pasteur who awakened the scientific world's interest in germs and bacteria. He wondered what became of them when people died. Did they contaminate the graveyard? Did they die with the host? So, he and one of his assistants went into the graveyard and took specimens of soil containing the remains of the deceased. Pasteur found, to his amazement, that germs introduced into such soil were soon killed. This strongly suggested to him that in the soil could be found the antagonist to the bacteria which caused disease in man.

Pasteur himself seems to have done no more work on this phenomenon. In 1885, however, other papers of interest appeared. One of these was by Babés, who wrote that he had "studied experimentally the

way in which bacteria of a known species produce chemical substances or modify the culture medium in such a way as to harm bacteria of other species. If the study of the mutual antagonisms of bacteria were sufficiently far advanced, a disease caused by one bacterium could probably be treated by another."

Despite an enormous amount of work extending over 70 years, no antibiotic substance from a mold or bacterium had found an undisputed and permanent place in medicine.

But in 1928, Alexander Fleming, a bacteriologist at St. Mary's Hospital in London, trying to isolate *Staphylococcus aureus*, found that something strange was happening on one of the Petri dishes containing the bacteria.

Fleming removed the invading substance from the dish. He found it was alive. It was a mold of the *Penicillium* family. It produced a selective antibacterial substance which was freely diffusible in agar. Diffusibility is an important property in antiseptics. It inhibited the growth of and even killed many pathogenic bacteria. It was not toxic when injected into animals and had no irritant effect when applied to the human cornea or to large infected surfaces.

It was the first substance of its type encountered which did not destroy leukocytes. This action more than any other prompted Fleming to say in his first paper, "It may be an efficient antiseptic for application to or injection into, areas infected with penicillin-sensitive microbes."

Additional work by Clutterbuck, Lovell and Raistrick established penicillin as an organic acid, but in view of its great lability and the very low yields, work on penicillin was abandoned in favor of more promising projects.

In 1940, stimulated by the urgent need for better agents for the treatment of burns and other wounds, Drs. Howard Florey and Ernest Chain of Oxford University, with their collaborators, undertook the reinvestigation of penicillin. They cultivated Fleming's organism in surface culture on what amounted to a small pilot plant scale. By keeping a low temperature during their extraction procedure, they were able to concentrate the penicillin a thousandfold and produce a dry powder, a salt of penicillin, which had reasonable stability. This furnished the material which was used to demonstrate the phenomenal curative properties of this antibiotic.

Where the fermentation of acetone had come to the rescue of the

Western Powers in World War I, it was used again to produce a great life-saving weapon in the hands of the Allies in World War II in the production of penicillin, for fermentation is the very heart and soul of antibiotic manufacture.

Because of the virtual impossibility of quickly producing a significant amount of penicillin under war-time conditions in England, Florey and Heatley came to the United States in July 1941 in order to enlist the aid of the American government and pharmaceutical industry. Five commercial houses—Merck, Squibb, Pfizer, Abbott and Winthrop—were largely responsible for producing the penicillin which was used to establish it in modern therapy.

Incidentally, Squibb acquired penicillin in the first place by the merest fortunate accident. One of the British investigators, Howard Florey, coming over from England, ran into our own Dr. Geoffrey Rake. Dr. Rake had known the chap in school and was delighted to see him again. They got to talking shop and Dr. Rake discovered the reason for his friend's visit was to bring penicillin to this country. "Where are you going to take it?" Dr. Rake inquired. "Oh, maybe to Pfizer and some of the brewing companies. They have large vats and good fermentation facilities." "Oh, nonsense, bring it to Squibb, not the brewers; we'll make our own fermentation facilities," Dr. Rake answered. And *he* did, and *we* did and that is the casual, wonderful accident that preceded our obtaining the penicillin culture.

But first, numerous production problems had to be solved. Surface culture was responsible for the first commercial production of penicillin. Despite the fact that the process was expensive, laborious and commercially and economically impractical, it served to bridge the period between the initial interest in penicillin and the development of the submerged-culture process which answered quantity requirements.

Fermentation chemists and engineers learned to cultivate the mold in large aerated tanks. A new strain was found—*Penicillium chrysogenum*—which thrived in deep tanks and eventually gave 200 times more penicillin than Fleming's *P. notatum*. Feeding on a newly formulated liquid composed mainly of water in which corn had been steeped, the mold produced tons of the antibiotic.

Engineering techniques were devised to protect the fermentation culture from invasion by extraneous microbes which might contaminate an entire culture or, by fighting the *Penicillium* mold, reduce the yield.

Other techniques expedited the laborious process of recovering the antibiotic from the broth in which it was manufactured. The nutrient was changed again and again to increase the organism's activity and improve the proportion of penicillin which the organism would produce. By the war's end the United States was producing more than 7,000 billion units of penicillin a year. Now, U.S.A. production exceeds 500 trillion units per year; 2 billion doses at 250,000 U. per dose; 1,000,000 units for at least 500 million patients.

It is historically important to note here that the Germans never got beyond the Erlenmeyer flask stage of penicillin production during World War II. They did not understand the true significance of the British discoveries and when it did dawn on them, the air raids placed such construction out of the question.

With penicillin a success, scientists set out to find antibiotics capable of fighting diseases against which penicillin was ineffective. The molds, yeasts, actinomycetes, bacteria or similar microorganisms most likely to provide a new antibiotic were in the waters of lake, stream and sea—on the surface of the ground and beneath it—in the air to a height of three miles. The soil was the most promising source.

After several years of searching for an anti-microbial substance active primarily against gram-negative bacteria, Selman A. Waksman of Rutgers announced in 1944 the isolation of the antibiotic streptomycin. The microorganisms which produced streptomycin were identified as *Streptomyces griseus*. Streptomycin was active not only against gram-negative organisms, but was quite active against the mycobacteria.

Rapid progress was made in getting streptomycin to the physician for clinical investigation. Companies which took the initiative in getting streptomycin in production were Merck, who through fellowships at Rutgers University financed the original research on the drug, Abbott Laboratories, Heyden Chemical Corp., Eli Lilly, Charles Pfizer, Schenley Laboratories, E. R. Squibb & Sons and The Upjohn Company. While the government subsidized some of the penicillin development, the streptomycin program was financed entirely by industry at a cost of about $1,000,000.

Still the search went on. Aureomycin was discovered by Dr. Benjamin Duggar of the Lederle Laboratories and reported at a Conference on Aureomycin at the New York Academy of Sciences on July 21, 1948. It was obtained from *Streptomyces aureofaciens* and designated

Aureomycin because of the golden yellow produced in the moist substrate mycelium and the antibiotic itself. Aureomycin was the first of the broad-spectrum antibiotics, active against gram-positive and gram-negative bacteria and antagonistic to certain large viruses and Rickettsiae as well. Chloramphenicol discovered at Yale was developed by Parke, Davis about this time, and neomycin, a Waksman-Rutgers development, also came into the orbit about the same time.

Chemical investigation of Aureomycin and Terramycin revealed a relationship of their structures and the name tetracycline was proposed in 1952 for the basic structure common to both compounds. Tetracycline itself became available commercially in November 1953 and later was produced by a direct fermentation process. It is now commonly available as citrated or phosphorated compounds for greater effectiveness.

These and other important antibiotics were rapidly developed through fermentation techniques with early availability to the clinician, for specialized uses in medicine. Among these were nystatin, novobiocin, erythromycin, amphotericin and thiostrepton.

During the great vitamin development era of the past 40 years, pernicious anemia has been recognized as a nutritional deficiency closely associated with faulty assimilation. Certain foods, for example liver, when ingested in large quantities, served to alleviate this deficiency. Thus, for many years, highly refined liver hydrolysates were the only known treatment. In 1948, after several years of experimentation, Merck announced the crystallization from liver of the anti-pernicious anemia factor now known as vitamin B_{12}. It was purely by accident that this product was discovered to be a product of microbial fermentation. Merck and Squibb, working independently and at about the same time, found substantial quantities of vitamin B_{12} in the filtrates from cultures of *Streptomyces griseus* used to produce streptomycin. Today vitamin B_{12} is a major fermentation product of both companies and is produced by several types of microorganisms, principally bacteria and actinomycetes.

Antibiotics would have remained a laboratory curiosity had it not been for fermentation engineering. While it is true that antibiotics are made according to fermentation principles essentially the same as those of brewing, the practical problems are hardly comparable. Fermentation engineering is faced with the task of having to mass produce substances

which at the outset are available only in microscopic quantities. The yield extracted from the fermentation broth may represent only one ten-thousandth of the contents of the vat.

Bacteria, yeasts and molds feed upon organic materials. It is this feeding that interests the manufacturer; for if he supplies to certain yeasts, bacteria or molds the necessary fundamental energy food, together with other needed nutrients, then the microvegetative organisms will not only grow and multiply but will change the food into other chemical substances.

Fermentation under controlled conditions actually involves many chemical processes. Some of the more important ones are: *oxidation*, (e.g., alcohol to acetic acid, sucrose to citric acid, and dextrose to gluconic acid); *reduction*, (e.g., aldehydes to alcohols); *hydrolysis*, (e.g., starch to glucose or sucrose to glucose and fructose); *esterification*, (e.g., hexose phosphate from hexose and phosphoric acid); *dehydrogenation*, (e.g., adding a double bond to a steroid).

These reactions have been accomplished by taking microorganisms out of their habitat and inducing them to produce substances of a quality and quantity inconceivable except under conditions set by engineering. In order to obtain a desired chemical, it may be necessary to modify the temperature, pressure, aeration, agitation and nutritive ingredients of the environment in which the microbes live, or select new strains in preference to those whose natural habitat may be a ditch or pasture.

Industrial microbiology has become a highly involved technology and the dollar volume of its product has risen sharply. It functions prominently in every research organization encountering biological problems and requires for maximum productivity the talents and training not only of bacteriologists but also such specialists as mycologists, biochemists, physicists, chemists and engineers.

Dextran, once a scourge to the sugar industry, clogging filters, retarding crystallization and generally hindering the recovery of sugar, was proved at the latter part of the 19th century to be of bacterial origin. Its usefulness as a plasma expander has brought it national and international prominence in recent years. It is a polysaccharide which results from the fermentation of sucrose by several bacterial species.

The realization of the importance in chemotherapy of cortisone and hydrocortisone stimulated the search for synthetic methods which would be less costly than the chemical synthesis using bile acids as the

raw material. One of the more costly operations in the chemical synthesis of cortisone is the introduction of oxygen in the eleven position of the steroid nucleus. Microbiological modifications were found that accomplished this and other steps in the synthesis.

A combination of microbiological and chemical treatments has led to steroids with even more biological activity than the naturally occurring substances. Several new and more potent glucocorticoids have emerged, most of which involve microbiological as well as chemical steps.

The enthusiastic microbiologist, biochemist, and fermentation engineer will say "nothing is impossible with microorganisms!" To be sure, it seems wise to temper this enthusiasm somewhat, but most certainly the rapid progress of the last 15 to 20 years portends great things for the future. The synthetic organic chemist who one day frowned on the use of microorganisms, for example, in the early days of penicillin development, has come to regard these ingenious creatures with profound respect. He is turning to them to accomplish in a simple process and under mild reaction conditions, what he, the chemist, either cannot do at all or can only do as a result of costly multi-step processes.

In this connection it seems certain that most of the fruitful future developments in fermentation will be in two principal areas:

1. The total synthesis of extremely complex, useful organic compounds by microorganisms, and
2. The transformation of organic compounds to other molecules of greater value, using microorganisms to accomplish classical chemical reactions such as oxidation, reduction, esterification, and hydrolysis. Examples of total synthesis are penicillin, streptomycin and other antibiotics; examples of molecular transformations are the recent development of modified cortisones with extra features of potency and safety so helpful to the discriminating physician.

Through just two procedures, total synthesis and molecular transformation, the microorganisms are our favorite "little scientists" that will make significant contributions to some of our leading medical problems—virus diseases, cancer, mental diseases, hormone deficiencies, nutritional deficiencies, degenerative diseases, and many others.

The striking chemotherapeutic advances of the last decade and a half have resulted from comprehensive screening programs. Com-

parable progress in the development of new agents on the basis of theoretical considerations will be made as microbiological research, now steadily moving forward by the collaborative efforts of government, universities, foundations and industry, reaps the harvest of its investigation of cellular effects and selective toxicity of the known agents.

The long, long history of man's endeavor to arrange and control the fermentation process has found fascinated friends among the research scientists in the drug houses of 1958. In their hands, this past century, especially the most recent decade, is but a prelude to the exciting future that fermentation processes will open to all of us who are dedicated to serving the medical profession.

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Monday October 5

PHYSIOLOGY AND THERAPY OF THE GASTRECTOMIZED PATIENT

Chairman: THOMAS P. ALMY, *Cornell University Medical College*

LECTURES — 8:30 P.M.

CONTRIBUTIONS OF MOLECULAR BIOLOGY TO MEDICINE

FRANCIS O. SCHMITT, *Massachusetts Institute of Technology*

THE ESSENTIAL NATURE OF GLYCINE IN THE DYNAMICS OF THE CELL

DAVID RITTENBERG, Ph.D., *College of Physicians and Surgeons, Columbia University*

PANEL MEETING — 4 P.M.

Tuesday October 6

LONG-TERM RESULTS OF SURGERY FOR ACQUIRED CARDIOVASCULAR DISEASE

Chairman: CHARLES E. KOSSMANN, *New York University College of Medicine*

LECTURES — 8:30 P.M.

FACTORS INVOLVED IN CAUSING CONGENITAL MALFORMATIONS

JAMES G. WILSON, *University of Florida College of Medicine*

ADRENOGENITAL SYNDROME: ITS CAUSES, MANIFESTATIONS AND TREATMENT

LAWSON WILKINS, *The Johns Hopkins University School of Medicine*

CONTRIBUTIONS OF PNEUMOCOCCAL GENETICS TO FUNDAMENTAL PROBLEMS IN BIOLOGY

ROBERT AUSTRIAN, *State University of New York, Downstate Medical Center*

PANEL MEETING — 4 P.M.

Wednesday October 7

IATROGENICALLY INDUCED LIVER DISEASE

Chairman: GERALD KLATSKIN, *Yale University School of Medicine*

LECTURES — 8:30 P.M.

CELLULAR EFFECTS OF IONIZING RADIATION

HENRY S. KAPLAN, *Stanford University School of Medicine*

(continued on following page)

LECTURES — 8:30 P.M. (continued)

Wednesday October 7 *(continued)*

NEWER METABOLIC ASPECTS OF TRAUMA
JOHN M. KINNEY, *Harvard Medical School*

THE RELATION OF ENDOTOXIN TO FEVER AND SHOCK
CHANDLER A. STETSON, JR., *New York University College of Medicine*

PANEL MEETING — 4 P.M.

Thursday October 8

FERTILITY AND INFERTILITY
Chairman: JOHN ROCK, *Harvard Medical School*

LECTURES — 8:30 P.M.

GLYCOLYTIC PATHWAYS AND THEIR RELATIONSHIP TO LIPID METABOLISM
MARVIN D. SIPERSTEIN, *The University of Texas, Southwestern Medical School*

THE METABOLISM OF THE SERUM LIPOPROTEINS AND ITS RELATIONSHIP TO ATHEROSCLEROSIS
HOWARD A. EDER, *Albert Einstein College of Medicine*

THE PRESENT STATUS OF THE DIETARY FAT-SERUM LIPID PROBLEM
EDWARD H. AHRENS, *Jr., The Rockefeller Institute*

PANEL MEETING — 4 P.M.

Friday October 9

PROBLEMS IN HYPERSENSITIVITY
Chairman: H. SHERWOOD LAWRENCE, *New York University College of Medicine*

LECTURES — 8:30 P.M.

COPPER METABOLISM AND CERULOPLASMIN
I. HERBERT SCHEINBERG, *Albert Einstein College of Medicine*

IRON METABOLISM AND THE PATHOGENESIS OF IRON DEFICIENCY ANEMIA
CARL V. MOORE, *Washington University School of Medicine*

THE METABOLISM AND THE INTESTINAL TRANSPORT OF CALCIUM
DAVID SCHACHTER, *College of Physicians and Surgeons, Columbia University*

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THURSDAY December 17 1959	CURRENT CONCEPTS IN THE TREATMENT OF COMMON CONGENITAL HEART DEFECTS *Moderator:* JERE W. LORD, JR.
THURSDAY January 21 1960	THE FUNCTIONS OF THE HOSPITAL EMERGENCY ROOM *Moderator:* PRESTON A. WADE
THURSDAY February 18 1960	MANAGEMENT OF ALLERGIC STATES *Moderator:* HORACE S. BALDWIN
THURSDAY March 17 1960	TREATMENT OF COMMON POISONS *Moderator:* HAROLD JACOBZINER
THURSDAY April 21 1960	PATHOGENESIS AND MANAGEMENT OF ASCITES *Moderator:* FRANKLIN M. HANGER

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August 13—SOME MECHANISMS OF BACTERICIDAL CHEMOTHERAPEUTIC ACTION—Bernard D. Davis, *Professor of Bacteriology and Immunology, Harvard Medical School*

OBSERVATIONS ON THE NATURE OF STAPHYLOCOCCAL INFECTIONS—David E. Rogers, *Associate Professor of Medicine, Cornell University Medical College*

August 20—CURRENT THERAPY OF PULMONARY TUBERCULOSIS—(Panel) John H. McClement, *Moderator, Associate Professor of Medicine, College of Physicians and Surgeons, Columbia University,* Aaron D. Chaves, *Assistant Clinical Professor of Medicine and Assistant Professor of Clinical Public Health and Preventive Medicine at Cornell University Medical College,* Aaron Himmelstein, *Assistant Clinical Professor of Surgery, College of Physicians and Surgeons,* Columbia University

August 27—THE SIGNIFICANCE OF MAJOR CONTRIBUTIONS IN THE DEVELOPMENT OF ANTICOAGULANTS—Irving S. Wright, *Professor of Clinical Medicine, Cornell University Medical College*

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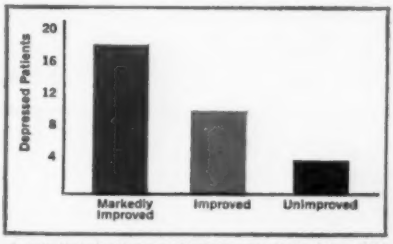
new psychoactive agent

Catron

β-phenylisopropyl hydrazine supplied as the hydrochloride

Revitalizes depressed patients—elevates mood, increases alertness and ability to maintain work and social adjustment.[1,2]



1. Agin, H. V.: In A Pharmacologic Approach to the Study of the Mind, Springfield, Ill., Charles C Thomas, in press.
2. Agin, H. V.: Conference on Amine Oxidase Inhibitors, New York Academy of Sciences, Nov. 20-22, 1958.

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Phenobarbital	3/8 grs. (24 mg.)
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In the current year the Committee on Medical Education will award *one* Scholarship grant in the amount of $4,500.00 for the *academic year 1960-1961.*

This Scholarship was established by the donor to provide aid for advanced study abroad in a clinical subject in preparation for the practice of medicine or surgery in any of their branches.

As stipulated by the donor of the fund, candidates must be *male* interns or residents in voluntary, municipal or Veterans Administration Hospitals in New York City.

The course of study, the auspices under which it is to be taken and the place or places where the study is to be pursued must receive the approval of the Committee. Applicants are favored who, from their records, show themselves capable of advanced work in clinical medicine. The Committee stipulates that the study be pursued abroad, preferably in Great Britain or in Continental Europe.

Applications for this Scholarship must be submitted by *SEPTEMBER 1, 1959.*

Candidates may secure application forms by addressing:

The Executive Secretary
Committee on Medical Education
The New York Academy of Medicine
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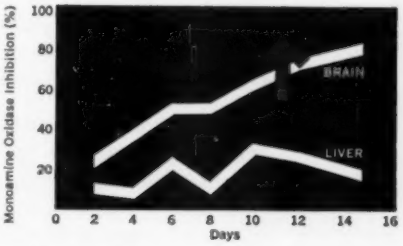
new psychoactive agent

Catron

β-phenylisopropyl hydrazine supplied as the hydrochloride

Brightens mood, dispels apathy, melancholy, social withdrawal through selective suppression of monoamine oxidase (MAO) of brain at doses which have little or no effect on liver.



Horita, A.: Report, Mar. 17, 1959

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This volume is arranged by subject with a separate author index and lists approximately 2900 references to review articles in clinical and experimental medicine and allied fields in all of the current journals received by the National Library of Medicine.

NOTICE

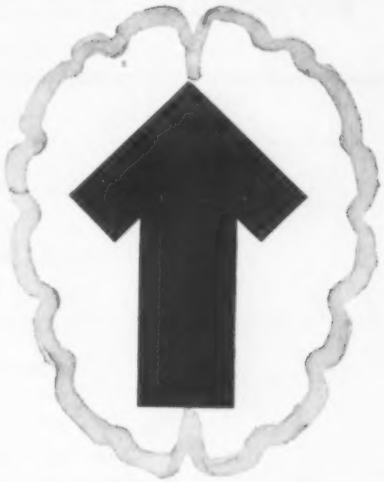
An exchange of correspondence between the Secretary of the Royal Society of Medicine in London, England, and the Director of The New York Academy of Medicine, was published in the July 1959 issue of the Bulletin (see page 472). In substance, this correspondence extends the hospitality and facilities of the two organizations to its respective membership visiting in either country.

Since publication of this correspondence, the Royal Society of Medicine has sent to the Academy a limited number of application blanks for "affiliated membership" for exclusive use of Fellows of The New York Academy of Medicine. Interested Fellows may apply to the Secretary, Committee on Medical Education, The New York Academy of Medicine, 2 East 103 Street, New York 29, if they wish to receive this form.

new psychoactive agent

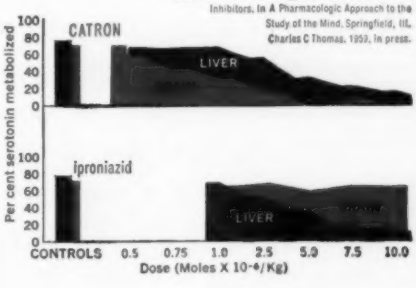
Catron

β-phenylisopropyl hydrazine supplied as the hydrochloride



Elevates mood, brightens outlook by raising levels of mood-controlling neurohormones, serotonin and norepinephrine . . . at doses which have little or no effect on the liver.

Horita, A.: The Pharmacology of the Monoamine Oxidase Inhibitors. In A Pharmacologic Approach to the Study of the Mind. Springfield, Ill., Charles C Thomas, 1959. In press.



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October 5 — 9, inclusive

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All inquiries should be addressed to:

Secretary, Postgraduate Week

THE NEW YORK ACADEMY OF MEDICINE

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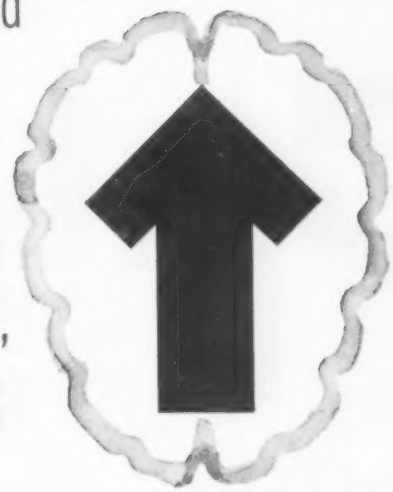
See pp. 541-543 for complete program

FELLOWS' PORTRAITS

It may not be generally known to Fellows of the Academy that the Library has an outstanding collection of medical portraits: some 10,200 separate ones mounted and about 139,300 catalogued in books and journals. It goes without saying that a picture of every Academy Fellow ought to be found here, and Fellows are invited to send the Library their photographs, if one is not already on file here. Any size is acceptable, from the vest-pocket up to the cabinet photograph. It is important that it be a clear print and a good likeness. Further, pictures of any other physicians for which Fellows wish to find a repository will be a welcome addition to the Library's collection.

withdrawn **apathetic** rejected **gloomy**
remorseful hopeless **listless** despairing
forlorn **somber** defeated
bitter crushed



WHEN THE WORDS MEAN DEPRESSION, THE TREATMENT IS

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Important new psychoactive agent—acts selectively on the brain to brighten outlook, raise spirits, rebuild self-esteem, revitalize depressed patients.

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For detailed information, request Brochure No. 19, CATRON

Important New

Catron®

β-phenylisopropyl hydrazine supplied as the hydrochloride

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How to use this new drug:

CATRON Hydrochloride is a monoamine oxidase (MAO) inhibitor useful in the treatment of depression and of other disorders indicated below. It is recommended for use in carefully selected cases and in those patients who have not responded to the milder drugs.

ADMINISTRATION AND DOSAGE

Dosage of CATRON must be individualized according to each patient's response. The initial daily dose should not exceed 12 mg. and should be reduced as soon as the desired clinical effect is obtained. In severe depressions some clinicians desire rapid results and begin treatment with 24 mg. daily: this dosage should not be continued for more than a few days. A single daily dose in the morning is recommended. A continuous or interrupted schedule may be used, the latter during the maintenance period.

DEPRESSION (Endogenous, Reactive, Postpartum, Involutional and Depression Secondary to Schizophrenic or Neurotic Reaction): initially, 12 mg. once daily for approximately 2 weeks, or less if improvement appears. Dosage is then reduced to 6 mg. daily. As improvement continues, maintenance dosage of 6 mg. every other day or of 3 mg. daily often proves satisfactory. An interrupted dose schedule is recommended for long-term therapy.

ANGINA PECTORIS—3 to 6 mg. daily in most cases. Relief of pain and elevation of mood may be dramatic. Victims of angina pectoris who respond in this manner should be cautioned against overexertion induced by their sense of well-being.

RHEUMATOID ARTHRITIS (Adjunctive Therapy—in severely disabling forms, particularly when accompanied by depression): 9 to 12 mg. daily for 3 days, then 6 mg. daily, reducing further to 3 mg. daily on signs of improvement. If a conventional antiarthritic agent is used, lower doses of each are indicated.

CAUTION

Certain circumstances should be watched carefully when using CATRON.

DRUG POTENTIATION—The list of drugs which CATRON potentiates is not yet complete. CATRON should not be used concomitantly with any other drug unless, (a) it has been ascertained that the two drugs bear no qualitative relationship, or (b) potentiating action is being sought, as may be the case with tranquilizing drugs including reserpine and the phenothiazines, and with the amphetamines, barbiturates and hypotensive agents.

HYPOTENSIVE EFFECT—All normotensive patients receiving CATRON, but especially elderly patients, should be warned about the possibility of orthostatic hypotension during the initial period of higher dosage. In the few instances where this may occur, lowering of the dose will usually permit continuation of therapy.

COLOR VISION—A reversible red-green color defect has been reported in a few patients, chiefly hypertensives, on ex-

Psychoactive Agent

- Brightens mood, diminishes apathy and confusion, curbs symptoms of withdrawal, self-pity, inadequacy, despair.[1,2]
- Acts selectively on brain at doses having little or no effect on liver.[5-7]
- Valuable in depressions associated with chronic diseases such as angina pectoris,[8] severe rheumatoid arthritis.[9]

For detailed information, request Brochure No. 19, CATRON

tended therapy with CATRON. Discontinue the drug if such changes occur.

ANIMALS, NEUROLOGIC SIGNS—In toxicity studies with animals, a neurologic syndrome has been observed characterized by tremors, muscle rigidity and difficulty in locomotion. Although extensive clinical experience has not shown such reactions to be a problem in humans in recommended dosage, should a similar neurologic disturbance occur, the possibility of drug action should be considered.

SIDE EFFECTS—Major side effects requiring cessation of therapy are infrequent. Other side effects—constipation, delay in starting micturition, increased sweating, hyperreflexia, ankle edema, blurring of vision, dryness of the mouth—are usually readily controlled by lowering the dosage. Rash, observed in a few patients, cleared up rapidly upon discontinuing therapy.

WARNING: Pharmacologic studies show that with proper dosage CATRON will inhibit monoamine oxidase in the brain without influencing this enzyme in the liver. This is in contrast to previous inhibitors, which depress monoamine oxidase activity in the liver before affecting this enzyme in the brain.

Although the evidence suggests that serious life-threatening hepatitis seen with other MAO inhibitors should not occur with CATRON in the recommended dosage, it has been reported on rare occasion with dosages in excess of the recommended levels.

The Following Precautions are Recommended:

1. In all instances daily dose should not exceed 12 mg.
2. Reduce daily dose as soon as response is established, usually in a matter of 1 to 2 weeks.
3. Do not prescribe to a patient more than sixteen 6 mg. tablets or thirty-two 3 mg. tablets of CATRON at one time.
4. Patient should return for observation before additional CATRON is prescribed. For this reason, prescriptions for CATRON should be marked, "not refillable."
5. Perform regular liver function tests.
6. Do not use the drug in patients with a history of viral hepatitis or other liver abnormalities.

CATRON is the original brand of β-phenylisopropyl hydrazine. It is supplied as the hydrochloride in tablets of 3 mg. and 6 mg., bottles of 50.

(1) Agin, H. V.: The Use of JB-516 (CATRON) in Psychiatry, Conference on Amine Oxidase Inhibitors, New York Academy of Sciences, Nov. 20-22, 1958. (2) Bercel, N. A.: A Pharmacologic Approach to the Study of the Mind, Springfield, Ill., Charles C Thomas, 1959, in press. (3) Kinross-Wright, J.: Panel Discussion of Psychic Energizers, *ibid.* (4) Kinross-Wright, J.: Experience with JB-516 (CATRON) and Other Psychochemicals in Clinical Practice, Conference on Amine Oxidase Inhibitors, New York Academy of Sciences, Nov. 20-22, 1958. (5) Horita, A., and Parker, R. G.: Comparison of Monoamine Oxidase Inhibitory Effects of Iproniazid and Its Phenyl Congener, Proc. Soc. Exper. Biol. & Med. **99**:617, 1958. (6) Horita, A.: *Beta*-Phenylisopropylhydrazine, A Monoamine Oxidase Inhibitor, Fed. Proc. **17**:379, 1958. (7) Horita, A.: The Pharmacology of the Monoamine Oxidase Inhibitors, In A Pharmacologic Approach to the Study of the Mind, Springfield, Ill., Charles C Thomas, 1959, in press. (8) Kennamer, R., and Prinzmetal, M.: Treatment of Angina Pectoris with CATRON (JB-516), Am. J. Cardiol. **3**:542, 1959. (9) Scherbel, A. L., and Harrison, J. W.: The Effects of Iproniazid and Some Other Amine Oxidase Inhibitors in Rheumatoid Arthritis, Conference on Amine Oxidase Inhibitors, New York Academy of Sciences, Nov. 20-22, 1958.

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Afternoon Panel Meetings — daily, at 4 p.m.

Scientific Exhibit

September 30 — October 9 (except Saturday and Sunday)

* * *

REGISTRATION

Members of the medical profession, including interns and residents, and those working in the allied sciences, are cordially invited to attend all sessions. Registration WITHOUT FEE is required for non-Fellows of the Academy

All inquiries should be addressed to:

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See pp. 541-543 for complete program

effective for constipation

Hospital Report Reveals Dannon Prune Whip Yogurt Successful in 95% of Chronic Cases When Taken Every Night for 3 Weeks

*An important study of chronic constipation at a New York hospital discloses these striking results:**

In a group of 194 chronically ill patients, averaging 71.6 years of age, regular feeding of Dannon Prune Whip Yogurt produced excellent results. Completely normal bowel habits were re-established in 187 patients, or 95.8%. They required no laxatives during the period of administration. Improvement in skin tone, seborrheic dermatitis, intestinal stasis and pruritus ani were also noted.

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*Forrer, F. P., and Boyd, L. J.: Am. J. Dig. Dis., 22:272, 1955

For literature, write Dannon Milk Products, Inc., 22-11 38th Avenue, Long Island City 1, N. Y.